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(54) **Prostaglandin derivatives for the treatment of glaucoma or ocular hypertension.**

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Description

The invention is concerned with the use of prostaglandin derivatives of PGA, PGB, PGE and PGF, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension. The invention relates also to ophthalmic compositions, containing an active amount of these prostaglandin derivatives, and the manufacture of such compositions.

Glaucoma is an eye disorder characterized by increased intraocular pressure, excavation of the optic nerve head and gradual loss of the visual field. An abnormally high intraocular pressure is commonly known to be detrimental to the eye, and there are clear indications that, in glaucoma patients, this probably is the most important factor causing degenerative changes in the retina. The pathophysiological mechanism of open angle glaucoma is, however, still unknown. Unless treated successfully glaucoma will lead to blindness sooner or later, its course towards that stage is typically slow with progressive loss of the vision.

The intraocular pressure, IOP (abbr. of intraocular pressure) can be defined as according to the formula:

$$IOP = P_e + F \times R \quad (1)$$

where P_e is the episcleral venous pressure, generally regarded as being around 9 mm Hg, F the flow of aqueous humor, and R the resistance to outflow of aqueous humor through the trabecular meshwork and adjacent tissue into Schlemm's canal.

Besides passing through Schlemm's, canal aqueous humor might also pass through the ciliary muscle into the suprachoroidal space and finally leave the eye through sclera. This uveoscleral route has been described for instance by Bill (1975). The pressure gradient in this case is insignificant compared to the gradient over the interior wall of Schlemm's canal and adjacent tissue in the former case. The flow limiting step along the uveoscleral route is assumed to be the flow from the anterior chamber into the supra-choroidal space.

A more complete formula is given by:

$$IOP = P_e + (F_t - F_u) \times R \quad (2)$$

where P_e and R are defined as above, F_t is the total outflow of aqueous humor and F_u is the fraction passing via the uveoscleral route.

IOP in human beings is normally in the range of 12 - 22 mm Hg. At higher values, for instance over 22 mm Hg, there is a risk that the eye may be affected. In one particular form of glaucoma, low tension glaucoma, damage may occur at intraocular pressure levels otherwise regarded as physiologically normal. The reason for this could be that the eye in these individuals is unusually sensitive to pressure. The opposite situation is also known, that some individuals may exhibit an abnormally high intraocular pressure without any manifest defects in the visual field or optic nerve head. Such conditions are usually referred to as ocular hypertension.

Glaucoma treatments can be given by means of drugs, laser or surgery. In drug treatment, the purpose is to lower either the flow (F) or the resistance (R) which, according to formula (1) above, will result in a reduced IOP; alternatively to increase the flow via the uveoscleral route which according to formula (2) also gives a reduced pressure. Cholinergic agonists, for instance pilocarpine, reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow (Crawford et al, 1987, and Nilsson et al, 1987). They do not appear, however to have any effect on the formation of aqueous humor or on the conventional outflow through Schlemm's canal (Crawford et al, 1987).

The use of prostaglandins and their derivatives is described for instance in US 4599353 and EP 87103714.9, and by Bito LZ et al (1983), Camras CB et al (1981, 1987a, 1987b, 1988), Giuffrè G (1985), Kaufman PL (1986), Kersetter JR et al (1988), Lee P-Y et al (1988) and VillumsenJ et al (1989).

Certain 11-substituted-16-phenoxy prostaglandin compounds of the PGE type have been disclosed in EP 170258, prostaglandin D_2 derivatives are disclosed in EP 253094, and 13,14-dihydro-15-keto prostaglandins, esp 20-alkyl substitued derivatives, are disclosed in EP 308135.

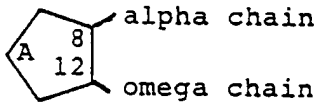
Woodward et al (1988 and 1989) concluded that studies on cat IOP revealed a substantial decrease for $PGF_{2\alpha}$ whereas identical doses of 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ and 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ were inactive.

It must be noticed however that even for substances which have been found to lower the intraocular pressure, that with respect to the practical usefulness of some of the previously described potentially useful

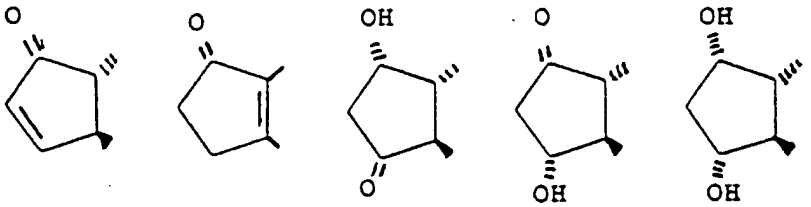
prostaglandins and derivatives, as suitable drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilation in the conjunctiva. It is probable, moreover, that prostaglandins have an irritant effect on the sensory nerves of the cornea. Thus local side effects will arise in the eye already when the amounts of prostaglandin administered are quite small-that is, already when the doses are lower than those that would be desirable for achieving maximum pressure reduction. It has thus been found, for instance, that for this reason it is clinically impossible to use $PGF_{2\alpha}$-1-isopropyl ester in the amount that would give maximum pressure reduction. Prostaglandins, being naturally occurring autacoids, are very potent pharmacologically and affect both sensory nerves and smooth muscle of the blood vessels. Since the effects caused by administrations of $PGF_{2\alpha}$ and its esters to the eye, comprise in addition to pressure reduction also irritation and hyperemia (increased blood flow), the doses currently practicable in clinical tests are necessarily very low. The irritation experienced when $PGF_{2\alpha}$ or its esters are applied, consists mainly in a feeling of grittiness or of having a foreign body in one's eye, this being usually accompanied by increased lacrimation.

We have now found that a solution to the problems discussed above is the use of certain derivatives of prostaglandins A, B, E and F, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension.

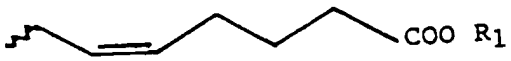
The prostaglandin derivatives have the general structure



wherein A represents the alicyclic ring C_8-C_{12} and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF A has the formula

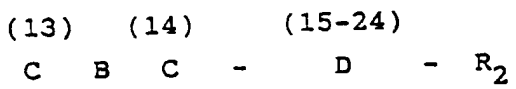


The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive concept. The alpha chain could typically be the naturally occuring alpha chain, which is esterified to the structure



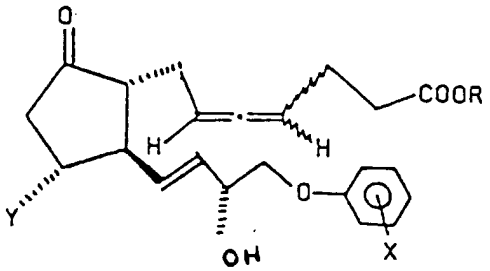
in which R_1 is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance metyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a C_6-C_{10} chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

The omega chain is defined by the following formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 1-10, preferably 2-8, and especially 2-5, and particularly 3 carbon atoms, optionally interrupted by preferably not more than two hetero atoms (O,S, or N), the substituent on each carbon atom being H, alkyl groups, preferably lower alkyl groups within 1-5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on C_{15} preferably being a carbonyl group, or (R)-OH or (S)-OH; each chain D containing preferably not more than three hydroxyl groups or not more than three carbonyl groups,
R_2 is a ring structure such as a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole
Certain 11-substituted-16-phenoxy prostaglandin compounds of the PGE type are as mentioned above disclosed in EP 170258 but the alpha chain, the cyclopentane ring as well as the omega chain were modified and there is no teaching towards the importance of modifying the omega chain to contain a phenyl group or an aromatic heterocyclic group, the concept of the present invention.

The compounds of Formula I of EP 170258



(I)

wherein R is hydrogen, lower alkyl; X is hydrogen, halo, trifluoromethyl,lower alkyl or lower alkoxy; Y is lower alkyl or

wherein Z is hydrogen, halo, methyl, methoxy or trifluoromethyl; and the wavy lines represent the α or β configuration with the provisio that when one wavy line is α the other is β,
are however disclaimed from the present invention.

Some examples on derivatives which were evaluated are the following (for structure information see Table I):

(1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropylester
(2) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(3) 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(4) 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropylester
(5) 17-phenyl-18,19,20-trinor-PGE_2-isopropylester

(6) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester
(7) 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(8) 16-[4-(methoxy)-phenyl]-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropylester
(9) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(10) 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-isopropylester
(20) 19-phenyl-20-nor-$PGF_{2\alpha}$-isopropylester

The most preferred derivatives at present are those in which the omega chain of the prostaglandin has the 18,19,20-trinor form, and especially the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms. Such derivatives are represented by (3), (6), (7) and (9) in the formulas given in Table I.

In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA, PGE or PGF, especially of PGA_2, PGE_2 and $PGF_{2\alpha}$
B is a single bond or a double bond
D is a carbon chain with 2-5, especially 3 atoms; C_{15} having a carbonyl or (S)-OH substituent and C_{16}-C_{19} having lower alkyl substituents, or preferably H
R_2 is a phenyl ring optionally having substituents selected among alkyl and alkoxy groups.

The invention thus relates to the use of certain derivatives of PGA, PGB, PGE and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represents a therapeutically more useful compound,

The method for treating glaucoma or ocular hypertension consists in contacting an effective intraocular pressure reducing amount of a composition, as aforesaid, with the eye in order to reduce the eye pessure and to maintain said pressure on a reduced level. The composition contains 0.1-30 µg, especially 1-10 µg, per application of the active substance i.e. a therapeutically active and physiologically acceptable derivative from the group defined above; the treatment may advantageously be carried out in that one drop of the composition, corresponding to about 30 µl, is administered about 1 to 2 times per day to the patient's eye. This therapy is applicable both to human beings and to animals.

The invention further relates to the use of therapeutically active and physiologically acceptable prostaglandin derivatives from the group defined above for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

The prostaglandin derivative is mixed with an ophthalmologically compatible vehicle known per se. The vehicle which may be employed for preparing compositions of this invention comprises aqueous solutions as e.g. physiological salines, oil solutions or ointments. The vehicle furthermore may contain ophthalmologically compatible preservatives such as e.g. benzalkonium chloride, surfactants like e.g. polysorbate 80, liposomes or polymers, for example methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

The invention is also related to ophthalmological compositions for topical treatment of glaucoma or ocular hypertension which comprise an effective intra ocular pressure reducing amount of a prostaglandin derivative as defined above and an ophthalmologically compatible carrier, the effective amount comprising a dose of about 0.1-30 µ in about 10-50 µ of the composition.

In the experiments carried out in this investigation the active compound, in an amount, varying with potency of the drug, from 30 µg to 300 µg/ml was dissolved in a sterilized aqueous solution (saline 0.9 %) containing 0.5 % polysorbate-80 as solubilizing agent.

The invention is illustrated by means of the following non-limitative examples.

Synthesis of prostaglandin derivatives

Example 1: Preparation of 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropyl ester (1).

A 50 ml round bottom flask equipped with a magnetic stirring bar was charged with 17.5 mg (0.04 mmol) 16-phenyl-17,18,19,20-tetranor $PGF_{2\alpha}$ (Cayman Chemical), 5 ml CH_2Cl_2,30.2 mg (0.23 mmol) diisopropylethylamine. This solution was stirred at -10 °C and 13.5 mg (0.07 mmol) of isopropyltriflate (freshly prepared) was added. This solution was allowed to stand at -10 °C for 15 min and was then slowly warmed to room temperature. When the esterification was complete according to TLC (usually after 3-4 h at

room temperature) the solvent was removed in vacuo. The residue was diluted with 20 ml ethylacetate, washed with 2x10 ml 5 % sodium hydrogencarbonate and 2x10 ml 3 % citric acid. The organic layer was dried over unhydrous sodium sulfate. The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel-60 using ethyl acetate: aceton 2: 1 as eluent. The title compound was obtained as a colourless oily substance (71 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	3.3 (1H q)
2.8 (2H d)	5.0 (1H m)
3.8 (1H m)	5.3-5.7 (4H m)
4.1 (1H t)	7.1-7.3 (5H m)

Example 2: Preparation of 17-phenyl-18,19,20- trinor $PGF_{2\alpha}$-isopropyl ester (2).

A 50 ml round bottom flask equipped with a magnetic stirring bar was charged whith 20 mg (0.05 mmol) 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ (Cayman Chemicals), 6 ml acetone, 39.2 mg (0.25 mmol) DBU and 42.5 mg (0.25 mmol) isopropyl iodide. The solution was allowed to stand at room temperature for 24 h, the solvent was removed in vacuo and the residue was diluted with 30 ml of ethyl acetate, washed twice with 10 ml 5 % sodiumhydrogen carbonate and 10 ml 3 % citric acid. The solvent was removed in vacuo, and the crude product was chromatographed on silica gel-60 using ethyl acetate: acetone 2:1 as eluent. The title compound (2) was obtained as an oily substance (65 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	4.9 (1H m)
3.9 (1H m)	5.4-5.6 (4H m)
4.1 (1H t)	7.1-7.3 (5H m)
4.2 (1H m)	

Example 3: Preparation of 15-dehydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (3)

20.9 mg (0.092 mmol) DDQ was added to a solution of 10 mg (0.023 mmol) 17-phenyl-18,19,20 trinor $PGF_{2\alpha}$-isopropyl ester (2) in 8 ml dioxane. The reaction mixture immediately turned brown, the reaction mixture was stirred at room temperature for 24 h. The precipitate formed was filtered, washed with 10 ml ethyl acetate, the filtrate was diluted with 10 ml ethylacetate washed with 2x10 ml water, 2x10 ml NaOH IM and 20 ml brine. The organic layer was dried on unhydrous sodium sulfate and the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel using ethyl acetate: ether 1:1 as eluent. The title compound (3) was obtained as a colourless oily substance (76 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.0 (1H m)	6.2 (1H d)
4.2 (1H m)	6.7 (1H q)
5.0 (1H m)	7.1-7.3 (5H m)

Example 4: Preparation of 16-phenoxy-17,18,19,20 -tetranor $PGF_{2\alpha}$-isopropyl ester(4).

Following a procedure similar to that described in example 2 using 20 mg (0.051 mmol) 16-phenoxy-17,18,19,20 -tetranor $PGF_{2\alpha}$ (Cayman Chemicals). The crude product was purified by column chromatography on silica gel-60 using ethyl acetate: acetone 2:1 as eluent. The title compound (4) was an oily substance (53.2 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.4 (2H m)
3.9 (3H m)	5.7 (2H m)
4.2 (1H m)	6.9 (3H m)
4.5 (1H m)	7.3 (2H m)
5.0 (1H m)	

Example 5: Preparation of 17-phenyl-18,19,20-trinor PGE_2-isopropyl ester (5).

Following a procedure similar to that described in example 2 using 10 mg (0.026 mmol) 17-phenyl-18,19,20- trinor PGE_2 (Cayman Chemicals). The crude product was purified by column chromatography on silica gel-60 using ether as eluent. The title compound (5) was an oily substance (38.9 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.3 (2H m)
3.9-4.1 (2H m)	5.6 (2H m)
4.9 (1H m)	7.2 (5H m)

Example 6: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-isopropyl ester (6).

Following a procedure similar to that described in example 2 using 10 mg (0.026 mmol) 13,14-dihydro-17-phenyl PGA_2(Cayman Chemicals). The crude product was chromatographed on silica gel-60 using ether as eluent. The title compound (6) was an oily substance (48 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.3 (1H m)	7.3 (5H m)
5.0 (1H m)	

Example 7: Preparation of 15-(R)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (7). (Table II)

7.1 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-(3-oxo-5-phenyl-1-trans-pentenyl)-7-(R)-(4-phenylbenzoyloxy)-cis-bicyclo [3,3,0] octane (13).

18 g (0.05 mol) alcohol (11), 32 g (0.15 mol) DCC, 39.1 g (0.5 mol) DMSO (newly distilled from CaH_2) and 30 ml DME were charged to a 200 ml flask under nitrogen. Orthophosphoric acid was added in one portion, and an exothermic reaction occured. The reaction mixture was stirred mechanically at room temperature for 2h, and the resultant precipitate was filtered and washed with DME. The filtrate (12) can be used directly for Emmon condensation reaction.

To a suspension of 1.2 g (0.04 mol) NaH (80 % washed with n-pentane to remove mineral oil) in 100 ml DME under nitrogen was added dropwise 12.3 g (0.048 mol) dimethyl-2-oxo-4-phenylbutyl-phosphonate in 30 ml DME. The mixture was stirred mechanically for 1h at room temperature, then cooled to -10 °C and a solution of the crude aldehyde (12) was added in dropwise. After 15 min at 0 °C and 1h at room temperature the reaction mixture was neutralized with glacial acetic acid, the solvent was removed under vacuum, and to the residue was added 100 ml ethyl acetate, washed with 50 ml water and 50 ml brine. The organic layer was dried over unhydrous sodium sulfate. The solvent was removed in vacuo and the resulting white precipitate filtered and washed with cold ether. The title compound (13) was obtained as a crystalline substance mp 134.5-135.5 (53 % yield).

7.2 Preparation of 1-(S)-2-oxa-3oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-(4-phenylbenzoyloxy) cis-bicyclo [3,3,0]octane (14).

10 g (0.021 mol) enone (13) and 3.1 g (0,008 mol) cerous-chloride heptahydrate in 50 ml methanol and 20 ml CH_2Cl_2 were charged to a 200 ml round bottom flask equipped with a magnetic stirring bar and was cooled to -78 °C under nitrogen. Sodium borohydride was added in small portions, after 30 min the reaction mixture was quenched by addition of saturuted NH_4Cl, and extracted with 2x50 ml ethyl acetate. The extracts were dried and concentrated to leave a colourless oil (98 % yield).

7.3 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo-[3,3,0] octane (15).

To a solution of 9.8 g (0.02 mol) lactone (14) in 100 ml absolute methanol was added 1.7 (0.012 mol) potassium carbonate. The mixture was stirred with a magnetic bar, at room temperature. After 3 h the mixture was neutralized with 40 ml HCl 1 M, and extracted with 2x50 ml ethyl acetate. The extracts were then dried on unhydrous sodium sulfate and concentrated. The crude product was chromatographed on silica gel using ethyl acetate: acetone as eluent. The title compound (15) was obtained as an oily substance (85 % yield).

7.4 Preparation of 1-(S)-2-oxa-3-hydroxy-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo[3,3,0] octane (16).

To a solution of 3g(0.011 mol) lactone (15) in 60 ml unhydrous THF, stirred magnetically and cooled to -78 °C, 4.5 g (0.0315 mol) DIBAL-H in toluene was added dropwise. After 2h the reaction mixture was quenched by addition of 75 ml methanol. The mixture was filtered,the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel-60 using ethyl acetate: acetone 1:1 as eluent. The title compound (16) was obtained as a semisolid substance (78 % yield).

7.5 Preparation of 15-(R,S)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$(17).

2.5 g (25 mmol) sodium methyl sulfinylmethide in DMSO (freshly prepared from sodium anhydride and DMSO) was added dropwise to a solution of 5.6 g (12.6 mmol) 4-caboxybutyl triphenyl-phosphonium bromide in 12 ml DMSO. To the resultant red solution of the ylide was added dropwise a solution of the 1.2 g (4.2 mmol) hemiacetal (16) in 13 ml DMSO, and the mixture was stirred for 1h. The reaction mixture was diluted with 10 g ice and 10 ml water and extracted with 2x50 ml ethyl acetate, whereafter the aqueous layer was cooled, acidified with HCl 1 M and extracted with ethyl acetate, and then the organic layer was dried and concentrated. The resulting crude product was a colourless substance. The purity of the title compound (17) was estimated by TLC on silica gel using ethyl acetate: acetone: acetic acid 1:1:0.2 v/v/v as eluent.

7.6 Preparation of 15-(R)-17-phenyl-18,19,20- trinor $PGF_{2\alpha}$-isopropyl ester (7).

The crude product (17) was esterified following a procedure similar to that described in example 2 the product was purified by column chromatography on silica gel-60 using ethyl acetate as eluent and the resulting mixture of C_{15} epimeric alcohol were separated.

The title compound (7) was obtained as a colourless oily substance (46 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H m) 3.9 (1H m) 4.15 (2H m) 4.95 (1H m)	5.4 (2H m) 5.6 (2H m) 7.2 (5H m)

Example 8: Preparation of 16-[4-(methoxy)phenyl]-17,18,19,20-tetranor $PGF_{2\alpha}$-isopropyl ester (8).

Following a procedure similar to that described in example 7 with modified step 7-2, the aldehyde 12 described in step 7-2 was reacted with dimethyl-2-oxo-3-[4-(methoxy)phenyl]-propylphosphonate and was purified by column chromatography on silica gel-60 using ethyl acetate: toluene 1:1 as eluent. A colourless oily substance was obtained (57 % yield).

The title compound 16-[4-(methoxy)phenyl]-17,18,19,20-tetranor $PGF_{2\alpha}$-isopropyl ester (8) was obtained as an oily substance, and purified by column chromatography on silica gel-60 using ethyl acetate as eluent (46 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.0 (1H m)
2.8 (2H d)	5.4 (2H m)
3.75 (3H S)	5.6 (2H m)
3.9 (1H m)	6.8 (2H d)
4.15 (1H m)	7.2 (2H d)
4.3 (1H m)	

Example 9: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (9).

Following a procedure similar to that described in example 7, with minor modification, 5 g (0.018 mol) enone (13) in 100 ml THF was reduced using 2.03 g 10 % pd/c under hydrogen atmosphere. After completion of the reaction (as determined by TLC on silica gel using ethylacetate: toluene 1:1 as eluent) the mixture was filtered on celite. The filtrate was concentrated in vacuo and an oily substance was obtained (86 % yield).

The final product 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester containing a mixture of C_{15} epimeric alcohols were separated by preparative liquid chromatography using 40 % CH_3CN in water v/v as eluent.

Nuclear Magnetic Renonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.0 (1H m)
3.6 (1H m)	5.4 (2H m)
3.9 (1H m)	7.2 (5H m)
4.15 (1H m)	

Example 10: Preparation of 18-phenyl-19,20-trinor $PGF_{2\alpha}$-isopropyl ester (10).

Following a procedure similar to that described in example (7) with modified step 7-2. The aldehyde (12) described in 7-2 was reacted with dimethyl-2-oxo-5-phenyl pentyl phosphonate gave a crystalline substance trans-enone lactone (67 % yield).

The final product 18-phenyl-19,20-dinor $PGF_{2\alpha}$-isopropyl ester (10) was purified by column chromatography on silica gel-60 using ethyl acetate as eluent gave a colourless oil (41 % yield).

1.2 (6H d)	5.0 (1H m)
3.95 (1H m)	5.4 (2H m)
4.10 (1H m)	5.6 (2H q)
4.20 (1H m)	7.2 (5H m)

Example 11: Preparation of 19-phenyl-20-nor-$PGF_{2\alpha}$-isopropyl ester (20).

Following a procedure similar to that described in example (7) with modified step (7-2).

The aldehyde (12) described in (7-2) was reacted with dimethyl-2-oxo-6-phenyl-hexylphosphonate gave a colourless oil trans-enone lactone (56 % yield).

The final product 19-phenyl-20-nor-$PGF_{2\alpha}$-isopropyl ester (20) was a colourless oil, and was purified by column chromatography on silica gel-60 using ethyl acetate as eluent (30 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)-ppm: δ	
1.2 (6H d)	5.0 (1H m)
2.6 (2H t)	5.4 (2H m)
3.9 (1H m)	5.5 (2H t)
4.1 (1H m)	7.2 (5H m)
4.2 (1H m)	

Studies of eye pressure lowering effect and adverse reactions

The intraocular pressure (IOP) was determined in animals with a pneumatonometer (Digilab Modular One™, Bio Rad), specially calibrated for the eye of the particular species. The cornea was anaesthetized with 1-2 drops of oxibuprocain before each IOP measurement. In healthy human volunteers IOP was measured with applanation tonometry or with an air puff tonometer (Keeler pulsair). For applanation tonometry either a pneumatonometer (Digilab) or Goldmann's applanation tonometer mounted on a slit lamp microscope was used. The cornea was anaesthetized with oxibuprocain before each measurement with applanation tonometry. No local anaesthesia was employed before measurement with the pulsair tonometer.

The ocular discomfort after application of the test substances was evaluated in cats. The behaviour of cats after topical application of the test drug was followed and ocular discomfort was graded on a scale from 0 to 3, 0 indicating complete absence of any signs of discomfort, and 3 indicating maximal irritation as obvious from complete lid closure.

Conjunctival hyperemia after topical application of the test substances was evaluated in rabbits. The conjunctiva at the insertion of the superior rectus muscle of the eye was inspected or photographed with regular intervals and the degree of hyperemia was later evaluated from the color photographs in a blind manner. Conjunctival hyperemia was evaluated on a scale from 0 to 4, 0 indicating complete absence of any hyperemia, and 4 indicating marked hyperemia with conjunctival chemosis.

For determination of the effects on the intraocular pressure, primarily monkeys (cynomolgus) were employed. The reason for this is that the monkey eye is highly reminiscent of the human eye and therefor, generally, drug effects are readily extrapolated to the human eye. However, the disadvantage of using the monkey eye as a model is that the conjunctiva in this species is pigmented making it impossible to evaluate conjunctival hyperemia and furthermore, the monkey eye is relatively insensitive to irritation. Therefore, the cat eye, being very sensitive to prostaglandins was used for evaluating ocular discomfort and the rabbit eye with pronounced tendency to hyperemic reactions was used for evaluating conjunctival and episcleral hyperemia.

It is evident from Table III that modification of the omega chain of the prostaglandin skeleton introduced new and unexpected features to the prostaglandins with respect to ocular irritation (discomfort). Particularly 17-phenyl,18,19,20-trinor-$PGF_{2\alpha}$-IE and analogs were unique in exhibiting a complete loss of ocular irritation with retained IOP lowering effect in monkeys. Whereas the 17-phenyl,18,19,20-trinor-$PGF_{2\alpha}$ derivatives were extremely well tolerated, 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE caused clear ocular discomfort although to a lesser degree than $PGF_{2\alpha}$-IE or 15-propionate-PGE_2-IE (Table III). However, substituting a hydrogen atom in the phenyl ring with a methoxy group having electron donating properties rendered the molecule practically free of ocular irritating effect, Table III. It is also evident from Table III that 18-phenyl-19,20,-dinor-$PGF_{2\alpha}$IE, 19-phenyl-20-nor-$PGF_{2\alpha}$-IE as well as 17-phenyl-18,19,20-trinor-PGE_2-IE and 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE, had no or very little irritating effect in the eye of cats. This indicates that the invention not only is valid for 16-, and 17-tetra- and trinor analogs of $PGF_{2\alpha}$ but for a range of omega chain modified and ring substituted analogs of $PGF_{2\alpha}$ (as exemplified with 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE to 19-phenyl-20-nor-$PGF_{2\alpha}$-IE), and more importantly even for different members of the prostaglandin family such as PGE_2 and PGA_2 modified in an analogous way (Table III). Thus, modifying the omega chain and substituting a carbon atom in the chain with a ring structure introduces completely new,

unexpected and advantageous qualities to naturally occuring prostaglandins in that the irritating effect in the conjunctiva and cornea is abolished. In the case of 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE exhibiting some irritating effect substituting a hydrogen atom in the ring structure with e.g. a methoxy group attenuates or abolishes the irritating effect.

In addition to the lack of ocular discomfort the omega chain modified analogs also exhibited an advantage over naturally occuring prostalgandins in that they caused considerably less conjunctival hyperemia as studied in the rabbit eye (Table IV). Particularly, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE,13,14-dihydro-17-phenyl-18,19,20-trinor--$PGF_{2\alpha}$-IE, and 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-IE were adventageous in this respect. Also 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-IE and 19-phenyl-20-nor-$PGF_{2\alpha}$-IE induced very little conjunctival hyperemia (TableIV).

The intraocular pressure lowering effect of omega chain modified and ring-substituted prostaglandin analogs is demonstrated in Table V. It can be seen that particularly 16-phenyl-tetranor and 17-phenyl-trinor prostaglandin analogs significantly reduced IOP in animal eyes (Table V). In all but two series of experiments cynomolgus monkeys were used. It is of particular interest to note that 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-derivatives exhibiting no ocular irritation and only modest conjunctival/episcleral hyperemia significantly lowered IOP in primates. It should furthermore be observed that both 16-phenyl-17,18,19,20-tetranor-PGF_{α}-IE, 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-IE and 19-phenyl-20-nor-PGF_{α}-IE reduced the intraocular pressure, thus, modification of the omega chain and substituting a carbon atom in the chain with a ring structure do not render the molecule inactive with respect to the effect on the intraocular pressure.

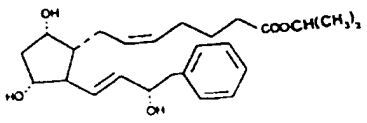
Furthermore, it should be observed that substituting a hydrogen on the ring structure of 16-phenyl,17,18,19,20-tetranor-$PGF_{2\alpha}$-IE with a methoxy group eliminated much of the ocular irritating effect preserving most of the intraocular pressure lowering effect. Thus, omega chain modified and ring substituted prostaglandin analogs reduce IOP effectively in animals. It is further demonstrated in Table V that 16-phenoxy-17,18,19,10-tetranor-$PGF_{2\alpha}$-IE effectively lowers the intraocular pressure as studied in cats. Thus, substituting carbon 17 in the omega chain with a hetero atom, in this case oxygen, does not render the molecule inactive with respect to the effect on IOP.

It is noteworthy that most of the 17-phenyl,18,19,20-trinor-prostaglandin analogs had poor intraocular pressure lowering effect in cats, even at high doses. It is to be observed that the doses at which compounds were used presented in Table III are lower than those e.g. in Table V. Doses presented in Table III should be explicitly compared with those of the naturally occuring prostaglandins in the same table. The same is true for Table IV. It is clear that with increasing dose side effects may increase. However, the doses of prostaglandin derivatives used in monkeys are comparatively similar to those used in human volunteers, (Table VI) being practically free of side effects.

The effect of some omega chain modified prostaglandin analogs, more specifically 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, and 18-phenyl-19-20-dinor-$PGF_{2\alpha}$-IE on the intraocular pressure of healthy human volunteers is demonstrated in Table VI. All compounds significantly reduced the intraocular pressure. It is particularly significant in this respect that none of the compounds had any significant irritating effect (ocular discomfort) and that 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE and 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE caused very little if any conjunctival/episcleral hyperemia in man. Thus, omega chain modified, and ring substituted prostaglandin analogs seem to be unique in that these compounds reduce IOP without causing significant ocular side effects such as hyperemia and discomfort.

The present invention thus describes a group of compounds exhibiting the unique property of causing insignificant ocular side effects while retaining the intraocular pressure lowering effect. From the foregoing it is evident that the crucial modification of the molecule is a ring structure in the omega chain. Furthermore, substituents in the ring structure and/or in the omega chain may be introduced in certain molecules still exhibiting some side-effects in the eye. Hetero atoms may also be introduced into the ring substituted omega chain. Presently, particularly 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-derivatives seem very promising for therapeutic use in glaucoma. From the scientific literature it is evident that PGE_2 and PGA_2 or their esters lower IOP in the monkey (see Bito et al, 1989). Clinical studies with PGE_2 have also been performed demonstrating IOP-lowering effect in man (Flach and Eliason (1988)). Thus, the analogy with $PGF_{2\alpha}$ and its esters lowering IOP in the primate eye is logic. It is most reasonable to assume that other prostaglandins with modified omega chain exhibit essentially the same properties as $PGF_{2\alpha}$ with modified omega chain, i.e. IOP lowering effect without side effects.

TABLE I.



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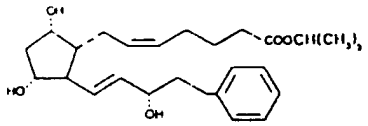

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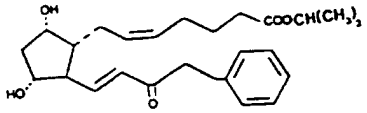

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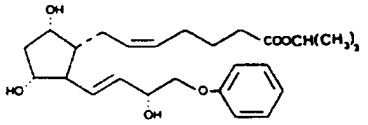

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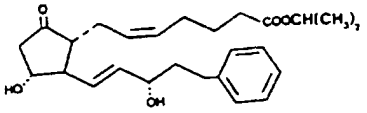

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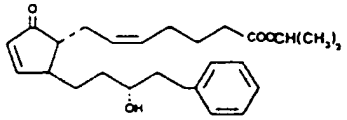

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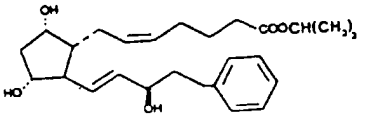

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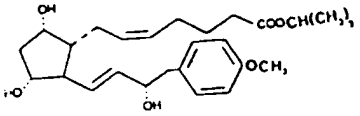

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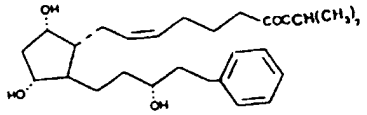

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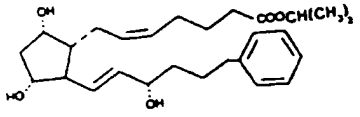

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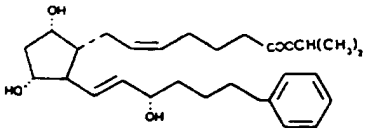

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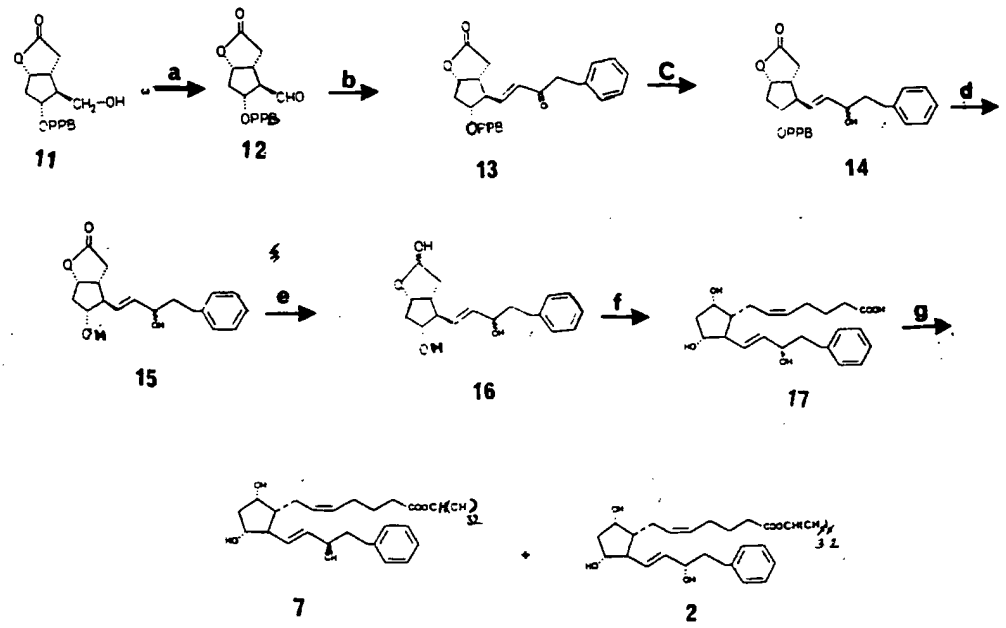
TABLE II.



Reagents:
a) DCC/DMSO/DME
b) NaH/ dimethyl-2-oxo-4-phenylbutyl phosphonate/DME
c) $CeCl_3.7H_2O$/$NaBH_4$/ CH_3OH/ -78°C
d) K_2CO_3/CH_3OH
e) DIBAL/-78°C
f) $NaCH_2SOCH_3$/
(4-carboxybutyl)-triphenylphosphonium bromide/DMSO
g) DBU/IprI/acetone

Table III. Irritative effect of naturally occuring prostaglandins ($PGF_{2\alpha}$, PGD_2 and PGE_2), and omega chain modified analogs applied as isopropylester on the cat eye. The avarage degree of discomfort was evaluated during 60 min after topical application of the respective test drug. The numbers within paranthesis refer to Table I.

Substance		Dose (µg)	Degree of occular irritation
$PGF_{2\alpha}$-isopropylester (-IE)		1	3.0 ± 0.0
15-propionate-PGE_2-IE		0.1-1	3.0 ± 0.0
15-propionate-PGD_2-IE		1	1.3 ± 0.2
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(2)	1-5	0
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(3)	5	0
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(7)	1-5	0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(9)	1	0
17-phenyl-18,19,20-trinor-PGE_2-IE	(5)	0.3	0
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE	(6)	1	0
16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	(1)	1	2.2 ± 0.3
16-[4-(methoxy)-phenyl]-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	(8)	1	0.2 ± 0.1
18-phenyl-19,20-dinor-$PGF_{2\alpha}$-IE	(10)	1	0.7 ± 0.1
19-phenyl-20-nor-$PGF_{2\alpha}$-IE	(20)	1	0.5 ± 0.1
16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	(4)	5	0.3 ± 0.2

Table IV. Degree of conjunctival hyperemia in the rabbit eye after application of naturally occuring prostaglandins ($PGF_{2\alpha}$, and PGE_2), and omega chain modified analogs applied as isopropylesters.

Substance		Dose (µg)	Degree of hyperemia
$PGF_{2\alpha}$-isopropylester (-IE)		0.1	2.8 ± 0.2
15-propionate-PGE_2-IE		0.5	2.7 ± 0.3
16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	(1)	0.5	1.3 ± 0.9
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(2)	0.5	2.0 ± 0.3
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(3)	0.5	0.7 ± 0.3
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(7)	0.5	2.0 ± 0.0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE	(9)	0.5	1.3 ± 0.3
17-phenyl-18,19,20-trinor-PGE_2-IE	(5)	0.5	2.7 ± 0.2
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE	(6)	0.5	0.3 ± 0.3
18-phenyl-19,20-dinor-$PGF_{2\alpha}$-IE	(10)	0.5	0.3 ± 0.2
19-phenyl-20-nor-$PGF_{2\alpha}$-IE	(20)	0.5	0.2 ± 0.2
16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	(4)	0.5	2.3 ± 0.3

Table V. Intraocular pressure reducing effect of naturally occuring prostaglandin ($PGF_{2\alpha}$) and omega chain modified analogs as determined in cynomolgus monkeys or cats. Unless specified data were obtained in monkeys. The figures within parenthesis refer to formulas given in Table I.

* Indicates statistical significance $p < 0.05$. The substances were applied topically.
** Data obtained in cat eyes.

Substance	Dose (µg)	Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)
$PGF_{2\alpha}$-isopropylester (IE)	1.5	E 11.4±0.7	8.3±0.5 *	8.0±0.6 *	9.3±0.8
		C 11.0±0.7	10.7±0.4	10.1±0.4	10.6±0.9
16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE (1)	3.2	E 12.7±1.1	11.8±1.1	9.1±0.8 *	8.4±0.7 *
		C 12.8±0.5	14.0±0.2	13.0±0.8	11.7±0.8
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (2)	3.2	E 12.8±0.6	11.9±0.5	8.6±0.3 *	9.5±0.7
		C 13.4±0.6	11.7±0.6	12.4±0.2	11.9±0.7
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (9)	10.4	E 11.1±0.9	8.3±0.6	6.9±0.4 *	7.7±0.8
		C 10.6±0.7	8.8±0.9	10.3±1.1	9.5±1.0

Table V cont.

Substance	Dose (µg)		Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)
18-phenyl-19,20-dinor-$PGF_{2\alpha}$-IE	3.1 (10)		E 9.7±0.9	9.6±1.1	9.6±0.7	8.8±0.9 *
			C 10.1±1.0	9.4±1.2	9.8±1.2	9.4±0.9
16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	5 (4)	**	E 20.5±1.2	25.7±1.2	19.2±1.8	15.0±1.2 *
			C 20.7±1.2	22.7±1.1	19.5±0.9	19.2±0.8
16-[4-(methoxy)-phenyl]-17,18,19,20-tetranor-$PGF_{2\alpha}$-IE	3.2 (8)		E 11.2±0.9	10.5±1.3	9.8±1.4	9.2±0.9
			C 10.4±1.1	10.9±1.0	11.3±1.4 *	9.2±0.6
19-phenyl-20-nor-$PGF_{2\alpha}$-IE	1 (20)	**	E 16.9±1.0	16.6±0.7	15.8±0.8 *	18.1±1.2
			C 17.1±0.4	18.1±0.6	18.9±0.6	19.2±0.8

Table VI. Intraocular pressure reducing effect of different omega chain modified and ring substituted $PGF_{2\alpha}$-IE analogs in healthy human volunteers. The substance number is given within paranthesis.

* Indicates statistical significance $p < 0.05$.

Substance	Dose (µg)	n	Eye	Time after administration (hours) 0 (mmHg)	4 (mmHg)	6 (mmHg)	8 (mmHg)
17-phenyl-18,19,20-trinor-	1	4	Exp	11.9±1.7	11.0±0.9 *	10.1±0.7 *	9.8±0.7 *
$PGF_{2\alpha}$-isopropylester (IE) (2)			Contr	12.7±1.7	13.9±0.7	13.5±1.2	12.5±0.7
15-(R)-17-phenyl-18,19,20-	10	3	Exp	12.9±0.9	11.8±0.6	11.0±0.3	11.2±1.3 *
trinor-$PGF_{2\alpha}$-IE (7)			Contr	13.2±1.4	13.7±0.9	13.8±1.0	15.1±1.3
15-dehydro-17-phenyl-	10	4	Exp	17.7±0.6	14.6±0.2 *	13.6±0.7 *	-
18,19,20-trinor-$PGF_{2\alpha}$-IE (3)			Contr	17.5±0.7	16.4±0.5	16.3±1.0	-
13,14-dihydro-17-phenyl-	1	4	Exp	14.2±0.5	13.3±1.1	12.2±0.4 *	12.5±0.9
18,19,20-trinor-$PGF_{2\alpha}$-IE (9)			Contr	13.5±0.6	14.2±1.2	15.2±1.0	15.1±0.7
18-phenyl-19,20-dinor-	5	3	Exp	14.4±1.0	12.2±1.1	12.4±1.2	11.9±0.7 *
$PGF_{2\alpha}$-IE (10)			Contr	15.2±0.1	13.7±1.2	14.4±0.2	13.2±0.5

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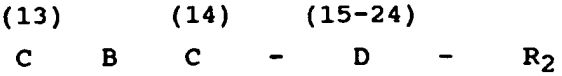
Woodward D F, Burke J A, Williams L S, Palmer B P, Wheeler L A, Woldemussie E, Ruiz G and Chen J (1989). Prostaglandin $F_{2\alpha}$ Effects on Intraocular Pressure Negatively Correlate with FP-Receptor Stimulation. Invest. Ophthalmol & Vis Sci 30(2):1838-1842.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB, PGE or PGF, in which the omega chain has the formula:



wherein

C is a carbon atom (the number is indicated within parenthesis)

B is a single bond, a double bond or a triple bond

D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group

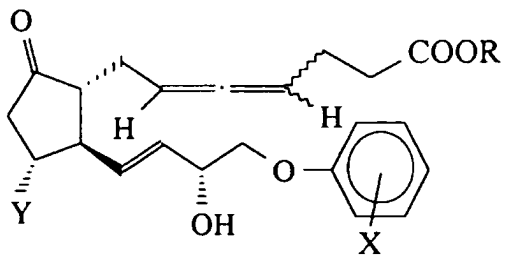
R_2 is a

(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a phenyl group; or

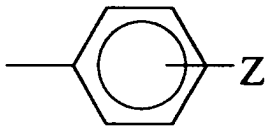
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiasol, imidazole, pyrrolidine, thiophene and oxazole;

with the exclusion of

- 11-substituted-16-phenoxy-PGE derivatives of the formula



wherein R is hydrogen, lower alkyl; X is hydrogen, halo, trifluoromethyl,lower alkyl or lower alkoxy; Y is lower alkyl or



wherein Z is hydrogen, halo, methyl, methoxy or trifluoromethyl; and the wavy lines represent the α or β configuration with the provisio that when one wavy line is α the other is β,
for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to anyone of claims 1 and 2, wherein D is a chain with 2-8 carbon atoms.

4. Use according to claim 3 wherein D is a chain with 2-5 carbon atoms.

5. Use according to claim 4 wherein D is a chain with 3 carbon atoms.

6. Use according to anyone of claims 1-5 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

7. Use according to anyone of claims 1-6 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

8. Use according to claim 6 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

9. Use according to claim 8 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

10. Use according to claim 9 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA, PGE or PGF.

11. Use according to claim 9 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA, PGE or PGF

12. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

14. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

15. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

16. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

17. Use according to claim 2, wherein the prostaglandin derivative is 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

18. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-PGE_2-alkyl ester with 1-10 carbon atoms.

19. Use according to claim 2, wherein the prostaglandin derivative is 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

20. Use according to claim 2, wherein the prostaglandin derivative is 19-phenyl-20-nor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

21. Use according to anyone of claims 12 to 20, wherein the ester of the prostaglandin derivative is the isopropylester.

22. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

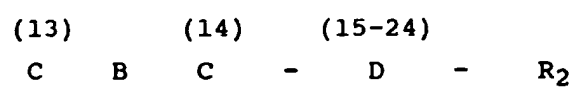
23. 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

24. 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

25. 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-isopropylester.

26. 19-phenyl-20-nor-$PGF_{2\alpha}$-isopropylester.

27. An ophthalmological composition for topical treatment of glaucoma or ocular hypertension which comprises an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB, PGE or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents

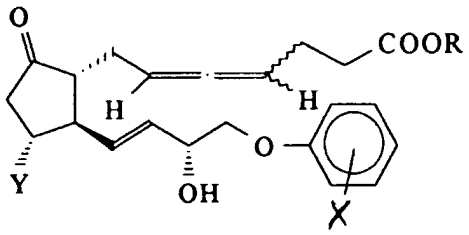
on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,

R_2 is

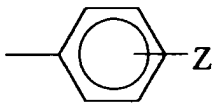
(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or

(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

with the exclusion of compositions containing 11-substituted-16-phenoxy-PGE derivatives of the formula



wherein R is hydrogen, lower alkyl; X is hydrogen, halo, trifluoromethyl,lower alkyl or lower alkoxy; Y is lower alkyl or



wherein Z is hydrogen, halo, methyl, methoxy or trifluoromethyl; and the wavy lines represent the α or β configuration with the provisio that when one wavy line is α the other is β,
in an ophthalmologically compatible carrier.

28. An ophthalmological composition according to claim 27 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

29. An ophthalmological composition according to claim 27 in which the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

30. An ophthalmological composition according to claim 27 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

31. An ophthalmological composition according to claim 27 in which the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

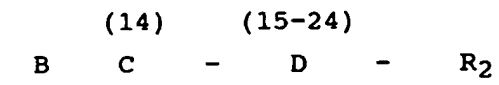
32. An ophthalmological composition according to claim 27 in which the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

33. An ophthalmological composition according to anyone of claims 27 to 31 containing 0.1-30 µg of the prostaglandin derivative

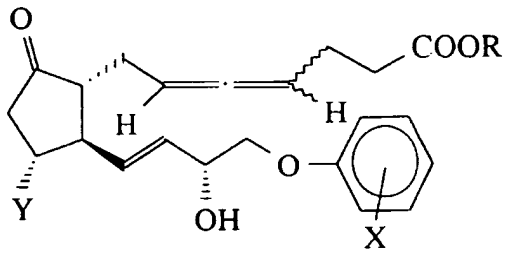
34. An ophthalmological composition according to claim 32 containing 1-10 µg of the prostaglandin derivative.

Claims for the following Contracting States : ES, GR

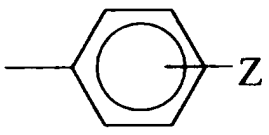
1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB, PGE or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group
R_2 is a
(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;
with the exclusion of
- 11-substituted-16-phenoxy-PGE derivatives of the formula



wherein R is hydrogen, lower alkyl; X is hydrogen, halo, trifluoromethyl,lower alkyl or lower alkoxy; Y is lower alkyl or



wherein Z is hydrogen, halo, methyl, methoxy or trifluoromethyl; and the wavy lines represent the α or β configuration with the provisio that when one wavy line is α the other is β,
for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to anyone of claims 1 and 2, wherein D is a chain with 2-8 carbon atoms.

4. Use according to claim 3 wherein D is a chain with 2-5 carbon atoms.

5. Use according to claim 4 wherein D is a chain with 3 carbon atoms.

6. Use according to anyone of claims 1-5 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

7. Use according to anyone of claims 1-6 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

8. Use according to claim 6 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

9. Use according to claim 8 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

10. Use according to claim 9 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA, PGE or PGF.

11. Use according to claim 9 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA, PGE or PGF

12. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

14. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

15. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

16. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

17. Use according to claim 2, wherein the prostaglandin derivative is 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

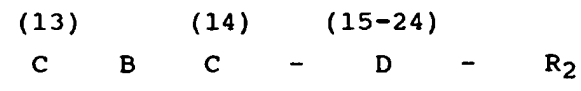
18. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-PGE_2-alkyl ester with 1-10 carbon atoms.

19. Use according to claim 2, wherein the prostaglandin derivative is 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

20. Use according to claim 2, wherein the prostaglandin derivative is 19-phenyl-20-nor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

21. Use according to anyone of claims 12 to 20, wherein the ester of the prostaglandin derivative is the isopropylester.

22. Method for producing an ophthalmological composition for topical treatment of glaucoma or ocular hypertension comprising admixing an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB, PGE or PGF, in which the omega chain has the formula:



wherein

C is a carbon atom (the number is indicated within parenthesis)

B is a single bond, a double bond or a triple bond

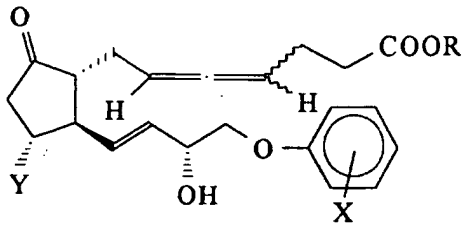
D is a chain with 1-10 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,

R_2 is

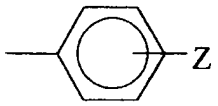
(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or

(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

with the exclusion of 11-substituted-16-phenoxy-PGE derivatives of the formula



wherein R is hydrogen, lower alkyl; X is hydrogen, halo, trifluoromethyl,lower alkyl or lower alkoxy; Y is lower alkyl or



wherein Z is hydrogen, halo, methyl, methoxy or trifluoromethyl; and the wavy lines represent the α or β configuration with the provisio that when one wavy line is α the other is β,
and an ophthalmologically compatible carrier.

23. Method according to claim 22 wherein the prostaglandin derivative is an ester.

24. Method according to any one of claims 22 and 23 wherein D is a chain with 2-8 carbon atoms.

25. Method according to claim 24 wherein D is a chain with 2-5 carbon atoms.

26. Method according to claim 25 wherein D is a chain with 3 carbon atoms.

27. Method according to any one of claims 22-26 wherein B is single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

28. Method according to any one of claims 22-27 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

29. Method according to claim 27 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

30. Method according to claim 29 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

31. Method according to claim 29 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative.

32. Method according to claim 23 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

33. Method according to claim 23 wherein the prostaglandin derivative is a 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

33. Method according to claim 23 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

35. Method according to claim 23 wherein the prostaglandin derivative is a 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms

36. Method according to claim 23 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor-PGE_2-alkylester with 1-10 carbon atoms.

37. Method according to claims 23 wherein the prostaglandin derivative is 18-phenyl-19,20-dinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms

38. Mehtod according to claims 23 wherein the prostaglandin derivative is 19-phenyl-20-nor-$PGF_{2\alpha}$- alkyl ester with 1-10 carbon atoms

39. Method according to any one of claims 22 to 38 wherein the ester of the prostaglandin derivative is the isopropylester.

40. Method according to anyone of claims 22 to 39 wherein the amount of prostaglandin derivative is 0.1-30 µg.

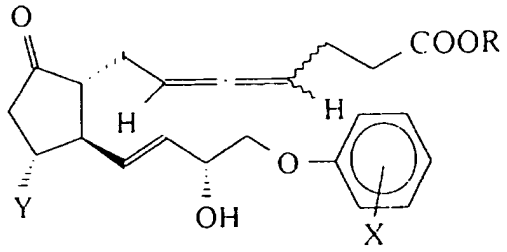
41. Method according to claim 40 wherein the amount of prostaglandin derivative is 1-10 µg.

Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

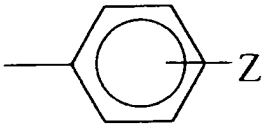
1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die Formel

$$\underset{(13)}{C}\quad\underset{}{B}\quad\underset{(14)}{C}\quad-\quad\underset{(15\text{-}24)}{D}\quad-\quad R_2$$

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,
unter Ausschluß von
- 11-substituierten-16-Phenoxy-PGE-Derivaten der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,
zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 und 2, dadurch **gekennzeichnet,** daß D eine Kette mit 2-8 Kohlenstoffatomen ist.

4. Verwendung nach Anspruch 3, dadurch **gekennzeichnet,** daß D eine Kette mit 2-5 Kohlenstoffatomen ist.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß D eine Kette mit 3 Kohlenstoffatomen ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, dadurch **gekennzeichnet,** daß B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

7. Verwendung nach einem der Ansprüche 1 bis 6, dadurch **gekennzeichnet,** daß R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

8. Verwendung nach Anspruch 6, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

9. Verwendung nach Anspruch 8, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

10. Verwendung nach Anspruch 9, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

11. Verwendung nach Anspruch 9, dadurch **gekennzeichnet**, daß das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

12. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkylester mit 1-10 Kohlenstoffatomen ist.

15. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

16. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

17. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

18. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-PGE_2-alkylester mit 1-10 Kohlenstoffatomen ist.

19. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

20. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 19-Phenyl-20-nor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

21. Verwendung nach einem der Ansprüche 12 bis 20, dadurch **gekennzeichnet,** daß der Ester des Prostaglandinderivats der Isopropylester ist.

22. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

23. 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

24. 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

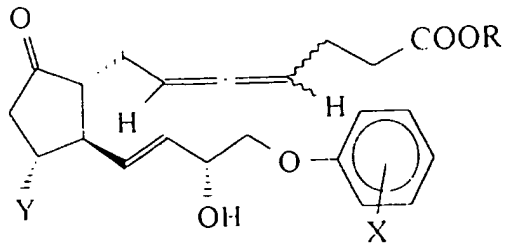
25. 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-isopropylester.

26. 19-Phenyl-20-nor-$PGF_{2\alpha}$-isopropylester.

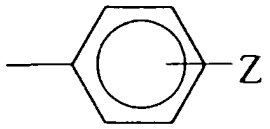
27. Ophthalmologisches Präparat zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, umfassend eine wirksame, den Augeninnendruck reduzierende Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die folgende Formel

$$\underset{C}{(13)} \quad \underset{B}{} \quad \underset{C}{(14)} \quad - \quad \underset{D}{(15\text{-}24)} \quad - \quad R_2$$

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,
unter Ausschluß von Präparaten, enthaltend 11-substituierte-16-Phenoxy-PGE-Derivate der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,
in einem ophthalmologisch verträglichen Träger.

28. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

29. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

30. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester ist.

31. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

32. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

33. Ophthalmologisches Präparat nach einem der Ansprüche 27 bis 31, umfassend 0,1-30 µg des Prostaglandinderivats.

34. Ophthalmologisches Präparat nach Anspruch 32, umfassend 1-10 µg des Prostaglandinderivats.

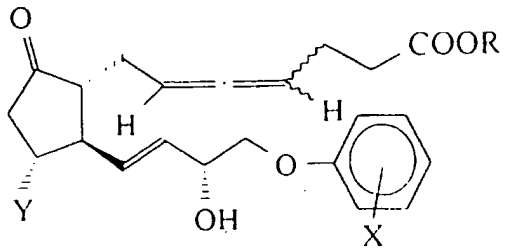
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die Formel

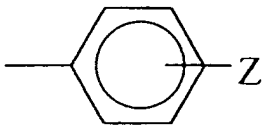
$$\underset{C}{\overset{(13)}{}} \quad \underset{B}{} \quad \underset{C}{\overset{(14)}{}} \quad - \quad \underset{D}{\overset{(15\text{-}24)}{}} \quad - \quad R_2$$

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,
unter Ausschluß von

- 11-substituierten-16-Phenoxy-PGE-Derivaten der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,
zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 und 2, dadurch **gekennzeichnet,** daß D eine Kette mit 2-8 Kohlenstoffatomen ist.

4. Verwendung nach Anspruch 3, dadurch **gekennzeichnet,** daß D eine Kette mit 2-5 Kohlenstoffatomen ist.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß D eine Kette mit 3 Kohlenstoffatomen ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, dadurch **gekennzeichnet,** daß B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

7. Verwendung nach einem der Ansprüche 1 bis 6, dadurch **gekennzeichnet,** daß R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

8. Verwendung nach Anspruch 6, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

9. Verwendung nach Anspruch 8, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

10. Verwendung nach Anspruch 9, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

11. Verwendung nach Anspruch 9, dadurch **gekennzeichnet,** daß das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

12. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkylester mit 1-10 Kohlenstoffatomen ist.

15. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

16. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

17. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

18. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-PGE_2-alkylester mit 1-10 Kohlenstoffatomen ist.

19. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

20. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 19-Phenyl-20-nor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

21. Verwendung nach einem der Ansprüche 12 bis 20, dadurch **gekennzeichnet,** daß der Ester des Prostaglandinderivats der Isopropylester ist.

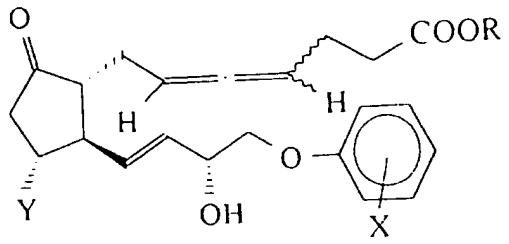
22. Verfahren zur Herstellung eines ophthalmologischen Präparats zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, dadurch **gekennzeichnet,** daß man eine wirksame, den Augeninnendruck reduzierende Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die Formel

$$\underset{(13)}{C}\quad\underset{}{B}\quad\underset{(14)}{C}\quad-\quad\underset{(15\text{-}24)}{D}\quad-\quad R_2$$

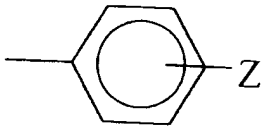
besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder

(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,

unter Ausschluß von 11-substituierten-16-Phenoxy-PGE-Derivaten der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,

und einen ophthalmologisch verträglichen Träger miteinander vermischt.

23. Verfahren nach Anspruch 22, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein Ester ist.

24. Verfahren nach einem der Ansprüche 22 und 23, dadurch **gekennzeichnet,** daß D eine Kette mit 2-8 Kohlenstoffatomen ist.

25. Verfahren nach Anspruch 24, dadurch **gekennzeichnet,** daß D eine Kette mit 2-5 Kohlenstoffatomen ist.

26. Verfahren nach Anspruch 25, dadurch **gekennzeichnet,** daß D eine Kette mit 3 Kohlenstoffatomen ist.

27. Verfahren nach einem der Ansprüche 22 bis 26, dadurch **gekennzeichnet,** daß B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

28. Verfahren nach einem der Ansprüche 22 bis 27, dadurch **gekennzeichnet,** daß R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

29. Verfahren nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

30. Verfahren nach Anspruch 29, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

31. Verfahren nach Anspruch 29, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat ist.

32. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

33. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

34. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

35. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

36. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-PGE_2-alkylester mit 1-10 Kohlenstoffatomen ist.

37. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

38. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 19-Phenyl-20-nor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

39. Verfahren nach einem der Ansprüche 22 bis 38, dadurch **gekennzeichnet,** daß der Ester des Prostaglandinderivats der Isopropylester ist.

40. Verfahren nach einem der Ansprüche 22 bis 39, dadurch **gekennzeichnet,** daß die Menge des Prostaglandinderivats 0,1-30 µg beträgt.

41. Verfahren nach Anspruch 40, dadurch **gekennzeichnet,** daß die Menge des Prostaglandinderivats 1-10 µg beträgt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :

$$\underset{(13)}{C}\ \underset{}{B}\ \underset{(14)}{C}\ -\ \underset{(15\text{-}24)}{D}\ -\ R_2$$

dans laquelle

C représente un atome de carbone (le numéro est inscrit entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

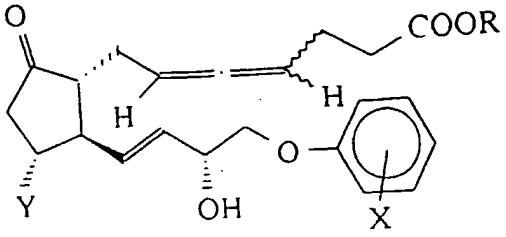
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

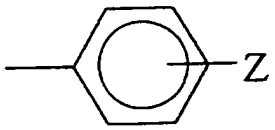
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion des dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans lequel Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant l'une quelconque des revendications 1 et 2, dans laquelle D représente une chaîne ayant 2 à 8 atomes de carbone.

4. Utilisation suivant la revendication 3, dans laquelle D représente une chaîne ayant 2 à 5 atomes de carbone.

5. Utilisation suivant la revendication 4, dans laquelle D représente une chaîne ayant 3 atomes de carbone.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

7. Utilisation suivant l'une quelconque des revendications 1 à 6, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

8. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

9. Utilisation suivant la revendication 8, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

10. Utilisation suivant la revendication 9, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

11. Utilisation suivant la revendication 9, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

15. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

16. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

17. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

18. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

19. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

20. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

21. Utilisation suivant l'une quelconque des revendications 12 à 20, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

22. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

23. Ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

24. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

25. Ester isopropylique de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

26. Ester isopropylique de 19-phényl-20-nor-$PGF_{2\alpha}$.

27. Composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, qui comprend une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :

$$\underset{(13)}{C}\quad\underset{(14)}{B}\quad\underset{(15\text{-}24)}{C - D - R_2}$$

dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 1 à 10 atomes de carbone, interrompue facultativement par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des

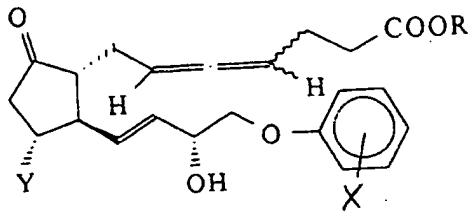
groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

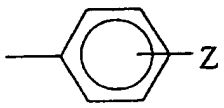
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion des compositions contenant des dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans laquelle Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

dans un véhicule ophtalmologiquement compatible.

28. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

29. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

30. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

31. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

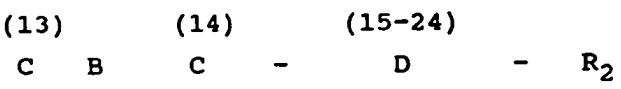
32. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

33. Composition ophtalmologique suivant l'une quelconque des revendications 27 à 31, contenant 0,1 à 30 µg du dérivé de prostaglandine.

34. Composition ophtalmologique suivant la revendication 32, contenant 1 à 10 µg du dérivé de prostaglandine.

Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

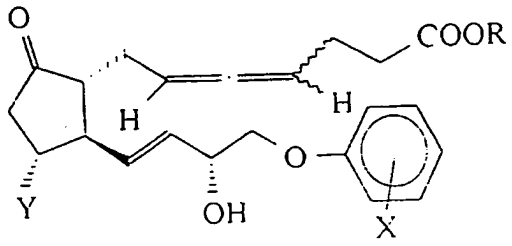
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

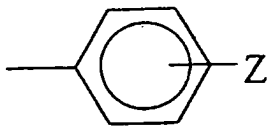
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion de dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans lequel Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant l'une quelconque des revendications 1 et 2, dans laquelle D représente une chaîne ayant 2 à 8 atomes de carbone.

4. Utilisation suivant la revendication 3, dans laquelle D représente une chaîne ayant 2 à 5 atomes de carbone.

5. Utilisation suivant la revendication 4, dans laquelle D représente une chaîne ayant 3 atomes de carbone.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

7. Utilisation suivant l'une quelconque des revendications 1 à 6, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

8. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

9. Utilisation suivant la revendication 8, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

10. Utilisation suivant la revendication 9, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

11. Utilisation suivant la revendication 9, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

15. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

16. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

17. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

18. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

19. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

20. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

21. Utilisation suivant l'une quelconque des revendications 12 à 20, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

22. Procédé de production d'une composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, comprenant le mélange d'une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :

dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

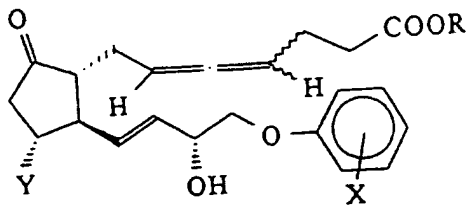
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

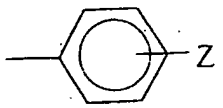
(i) un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et le groupe phényle : ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion de dérivés de 16-phénoxy-PGE substitués en position 11, de formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans laquelle Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

et un véhicule ophtalmologiquement compatible.

23. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est un ester.

24. Procédé suivant l'une quelconque des revendications 22 et 23, dans lequel D représente une chaîne ayant 2 à 8 atomes de carbone.

25. Procédé suivant la revendication 24, dans lequel D représente une chaîne ayant 2 à 5 atomes de carbone.

26. Procédé suivant la revendication 25, dans lequel D représente une chaîne ayant 3 atomes de carbone.

27. Procédé suivant l'une quelconque des revendications 22 à 26, dans lequel B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou bien est substitué avec un groupe (R)-OH ou (S)-OH.

28. Procédé suivant l'une quelconque des revendications 22 à 27, dans lequel R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle.

29. Procédé suivant la revendication 27, dans lequel le dérivé de prostaglandine est le dérivé à fonction 17-phényl-18,19,20-trinor.

30. Procédé suivant la revendication 29, dans lequel le dérivé de prostaglandine est le dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

31. Procédé suivant la revendication 29, dans lequel le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor.

32. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

33. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

34. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'α-alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF_2.

35. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

36. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

37. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

38. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est l'ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

39. Procédé suivant l'une quelconque des revendications 22 à 38, dans lequel l'ester du dérivé de prostaglandine est l'ester isopropylique.

40. Procédé suivant l'une quelconque des revendications 22 à 39, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 0,1 à 30 µg.

41. Procédé suivant la revendication 40, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 1 à 10 µg.

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(54) Prostaglandin derivatives for the treatment of glaucoma or ocular hypertension

Prostaglandinderivate zur Behandlung des grünen Stars oder einer okularen Hypertension

Dérivés de prostaglandine pour traitement du glaucome ou hypertension oculaire

(84) Designated Contracting States:
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- **Woodward D F, Burke J A, Williams L S, et al. 1989. "Prostaglandin F2a effects on intraocular pressure negatively correlate with FP receptor stimulation. Invest. ophtalmol & vis sci 30(2): 1838-1842**
- **Drugs of the future, 1992, 17(8), pp. 691-704**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 364 417 B2

Description

[0001] The invention is concerned with the use of prostaglandin derivatives of PGA, PGB, and PGF, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension. The invention relates also to ophthalmic compositions, containing an active amount of these prostaglandin derivatives, and the manufacture of such compositions.

[0002] Glaucoma is an eye disorder characterized by increased intraocular pressure, excavation of the optic nerve head and gradual loss of the visual field. An abnormally high intraocular pressure is commonly known to be detrimental to the eye, and there are clear indications that, in glaucoma patients, this probably is the most important factor causing degenerative changes in the retina. The pathophysiological mechanism of open angle glaucoma is, however, still unknown. Unless treated successfully glaucoma will lead to blindness sooner or later, its course towards that stage is typically slow with progressive loss of the vision.

[0003] The intraocular pressure, IOP (abbr. of intraocular pressure) can be defined as according to the formula:

$$IOP = P_e + F \times R \quad (1)$$

where P_e is the episcleral venous pressure, generally regarded as being around 9 mm Hg, F the flow of aqueous humor, and R the resistance to outflow of aqueous humor through the trabecular meshwork and adjacent tissue into Schlemm's canal.

[0004] Besides passing through Schlemm's, canal aqueous humor might also pass through the ciliary muscle into the suprachoroidal space and finally leave the eye through sclera. This uveoscleral route has been described for instance by Bill (1975). The pressure gradient in this case is insignificant compared to the gradient over the interior wall of Schlemm's canal and adjacent tissue in the former case. The flow limiting step along the uveoscleral route is assumed to be the flow from the anterior chamber into the suprachoroidal space.

[0005] A more complete formula is given by:

$$IOP = P_e + (F_t - F_u) \times R \quad (2)$$

where P_e and R are defined as above, F_I is the total outflow of aqueous humor and F_u is the fraction passing via the uveoscleral route.

[0006] IOP in human beings is normally in the range of 12 - 22 mm Hg. At higher values, for instance over 22 mm Hg, there is a risk that the eye may be affected. In one particular form of glaucoma, low tension glaucoma, damage may occur at intraocular pressure levels otherwise regarded as physiologically normal. The reason for this could be that the eye in these individuals is unusually sensitive to pressure. The opposite situation is also known, that some individuals may exhibit an abnormally high intraocular pressure without any manifest defects in the visual field or optic nerve head. Such conditions are usually referred to as ocular hypertension.

[0007] Glaucoma treatments can be given by means of drugs, laser or surgery. In drug treatment, the purpose is to lower either the flow (F) or the resistance (R) which, according to formula (1) above, will result in a reduced IOP; alternatively to increase the flow via the uveoscleral route which according to formula (2) also gives a reduced pressure. Cholinergic agonists, for instance pilocarpine, reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

[0008] Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow (Crawford et al, 1987, and Nilsson et al, 1987). They do not appear, however to have any effect on the formation of aqueous humor or on the conventional outflow through Schlemm's canal (Crawford et al, 1987).

[0009] The use of prostaglandins and their derivatives is described for instance in US 4599353 and EP 87103714.9, and by Bito LZ et al (1983), Camras CB et al (1981, 1987a, 1987b, 1988), Giuffrè G (1985), Kaufman PL (1986), Kersetter JR et al (1988), Lee P-Y et al (1988) and VillumsenJ et al (1989).

[0010] Certain 11-substituted-16-phenoxy prostaglandin compounds of the PGE type have been disclosed in EP 170258, prostaglandin D_2 derivatives are disclosed in EP 253094, and 13,14-dihydro-15-keto prostaglandins, esp 20-alkyl substitued derivatives, are disclosed in EP 308135.

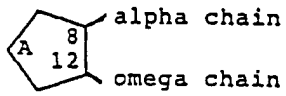
[0011] Woodward et al (1988 and 1989) concluded that studies on cat IOP revealed a substantial decrease for $PGF_{2\alpha}$ whereas identical doses of 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ and 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ were inactive.

[0012] It must be noticed however that even for substances which have been found to lower the intraocular pressure,

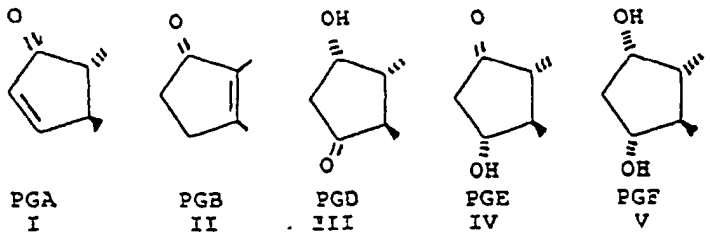
that with respect to the practical usefulness of some of the previously described potentially useful prostaglandins and derivatives, as suitable drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilation in the conjunctiva. It is probable, moreover, that prostaglandins have an irritant effect on the sensory nerves of the cornea. Thus local side effects will arise in the eye already when the amounts of prostaglandin administered are quite small-that is, already when the doses are lower than those that would be desirable for achieving maximum pressure reduction. It has thus been found, for instance, that for this reason it is clinically impossible to use $PGF_{2\alpha}$-1-isopropyl ester in the amount that would give maximum pressure reduction. Prostaglandins, being naturally occurring autacoids, are very potent pharmacologically and affect both sensory nerves and smooth muscle of the blood vessels. Since the effects caused by administrations of $PGF_{2\alpha}$ and its esters to the eye, comprise in addition to pressure reduction also irritation and hyperemia (increased blood flow), the doses currently practicable in clinical tests are necessarily very low. The irritation experienced when $PGF_{2\alpha}$ or its esters are applied, consists mainly in a feeling of grittiness or of having a foreign body in one's eye, this being usually accompanied by increased lacrimation.

[0013] We have now found that a solution to the problems discussed above is the use of certain derivatives of prostaglandins A, B, and F, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension.

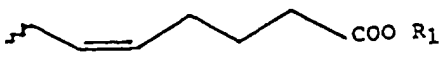
[0014] The prostaglandin derivatives have the general structure



wherein A represents the alicyclic ring C_8-C_{12} and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF A has the formula



The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive concept. The alpha chain could typically be the naturally occuring alpha chain, which is esterified to the structure



in which R_1 is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance metyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a C_6-C_{10} chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

[0015] The omega chain is defined by the following formula:

(13) (14)
C B C - D - R_2

wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by preferably not more than two hetero atoms (O,S, or N), the substituent on each carbon atom being H, alkyl groups, preferably lower alkyl groups within 1-5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on C_{15} preferably being a carbonyl group, or (R)-OH or (S)-OH; each chain D containing preferably not more than three hydroxyl groups or not more than three carbonyl groups,
R_2 is a ring structure such as a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole

[0016] Some examples on derivatives which were evaluated are the following (for structure information see Table I):

(1) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(2) 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(3) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester
(4) 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(5) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

The most preferred derivatives at present are the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms. Such derivatives are represented by (2), (3), (4) and (5) in the formulas given in Table I.

[0017] In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA or PGF, especially of PGA_2 and $PGF_{2\alpha}$
B is a single bond or a double bond
D is a carbon chain with 3 atoms; C_{15} having a carbonyl or (S)-OH substituent and C_{16}-C_{17} having lower alkyl substituents, or preferably H
R_2 is a phenyl ring optionally having substituents selected among alkyl and alkoxy groups.

[0018] The invention thus relates to the use of certain derivatives of PGA, PGB and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represents a therapeutically more useful compound, The method for treating glaucoma or ocular hypertension consists in contacting an effective intraocular pressure reducing amount of a composition, as aforesaid, with the eye in order to reduce the eye pessure and to maintain said pressure on a reduced level. The composition contains 0.1-30 µg, especially 1-10 µg, per application of the active substance i.e. a therapeutically active and physiologically acceptable derivative from the group defined above; the treatment may advantageously be carried out in that one drop of the composition, corresponding to about 30 µl, is administered about 1 to 2 times per day to the patient's eye. This therapy is applicable both to human beings and to animals.

[0019] The invention further relates to the use of therapeutically active and physiologically acceptable prostaglandin derivatives from the group defined above for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.
The prostaglandin derivative is mixed with an ophthalmologically compatible vehicle known per se. The vehicle which may be employed for preparing compositions of this invention comprises aqueous solutions as e.g. physiological salines, oil solutions or ointments. The vehicle furthermore may contain ophthalmologically compatible preservatives such as e.g. benzalkonium chloride, surfactants like e.g. polysorbate 80, liposomes or polymers, for example methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

[0020] The invention is also related to ophthalmological compositions for topical treatment of glaucoma or ocular hypertension which comprise an effective intra ocular pressure reducing amount of a prostaglandin derivative as defined above and an ophthalmologically compatible carrier, the effective amount comprising a dose of about 0.1-30 µ in about

10-50 μ of the composition.

[0021] In the experiments carried out in this investigation the active compound, in an amount, varying with potency of the drug, from 30 μg to 300 μg/ml was dissolved in a sterilized aqueous solution (saline 0.9 %) containing 0.5 % polysorbate-80 as solubilizing agent.

[0022] The invention is illustrated by means of the following non-limitative examples.

Synthesis of prostaglandin derivatives

Example 1: Preparation of 17-phenyl-18,19,20- trinor $PGF_{2\alpha}$-isopropyl ester (1).

[0023] A 50 ml round bottom flask equipped with a magnetic stirring bar was charged whith 20 mg (0.05 mmol) 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ (Cayman Chemicals), 6 ml acetone, 39.2 mg (0.25 mmol) DBU and 42.5 mg (0.25 mmol) isopropyl iodide. The solution was allowed to stand at room temperature for 24 h, the solvent was removed in vacuo and the residue was diluted with 30 ml of ethyl acetate, washed twice with 10 ml 5 % sodiumhydrogen carbonate and 10 ml 3 % citric acid. The solvent was removed in vacuo, and the crude product was chromatographed on silica gel-60 using ethyl acetate: acetone 2:1 as eluent. The title compound (2) was obtained as an oily substance (65 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	4.9 (1 H m)
3.9 (1 H m)	5.4-5.6 (4H m)
4.1 (1 H t)	7.1-7.3 (5H m)
4.2 (1 H m)	

Example 2: Preparation of 15-dehydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (2)

[0024] 20.9 mg (0.092 mmol) DDQ was added to a solution of 10 mg (0.023 mmol) 17-phenyl-18,19,20 trinor $PGF_{2\alpha}$-isopropyl ester (2) in 8 ml dioxane. The reaction mixture immediately turned brown, the reaction mixture was stirred at room temperature for 24 h. The precipitate formed was filtered, washed with 10 ml ethyl acetate, the filtrate was diluted with 10 ml ethylacetate washed with 2x10 ml water, 2x10 ml NaOH IM and 20 ml brine. The organic layer was dried on unhydrous sodium sulfate and the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel using ethyl acetate: ether 1:1 as eluent. The title compound (3) was obtained as a colourless oily substance (76 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.0 (1H m)	6.2 (1 H d)
4.2 (1H m)	6.7 (1H q)
5.0 (1 H m)	7.1-7.3 (5H m)

Example 3: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-isopropyl ester (3).

[0025] Following a procedure similar to that described in example 2 using 10 mg (0.026 mmol) 13,14-dihydro-17-phenyl PGA_2 (Cayman Chemicals). The crude product was chromatographed on silica gel-60 using ether as eluent. The title compound (6) was an oily substance (48 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.3 (1 H m)	7.3 (5H m)
5.0 (1 H m)	

Example 4: Preparation of 15-(R)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (4). (Table II)

4.1 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-(3-oxo-5-phenyl-1-trans-pentenyl)-7-(R)-(4-phenylbenzoyloxy)-cis-bicyclo [3,3,0] octane (13).

[0026] 18 g (0.05 mol) alcohol (11), 32 g (0.15 mol) DCC, 39.1 g (0.5 mol) DMSO (newly distilled from CaH_2) and 30 ml DME were charged to a 200 ml flask under nitrogen. Orthophosphoric acid was added in one portion, and an exothermic reaction occured. The reaction mixture was stirred mechanically at room temperature for 2h, and the resultant precipitate was filtered and washed with DME. The filtrate (12) can be used directly for Emmon condensation reaction.

[0027] To a suspension of 1.2 g (0.04 mol) NaH (80 % washed with n-pentane to remove mineral oil) in 100 ml DME under nitrogen was added dropwise 12.3 g (0.048 mol) dimethyl-2-oxo-4-phenylbutyl-phosphonate in 30 ml DME. The mixture was stirred mechanically for 1h at room temperature, then cooled to -10 °C and a solution of the crude aldehyde (12) was added in dropwise. After 15 min at 0 °C and 1h at room temperature the reaction mixture was neutralized with glacial acetic acid, the solvent was removed under vacuum, and to the residue was added 100 ml ethyl acetate, washed with 50 ml water and 50 ml brine. The organic layer was dried over unhydrous sodium sulfate. The solvent was removed in vacuo
and the resulting white precipitate filtered and washed with cold ether. The title compound (13) was obtained as a crystalline substance mp 134.5-135.5 (53 % yield).

4.2 Preparation of 1-(S)-2-oxa-3oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-(4-phenylbenzoyloxy) cis-bicyclo [3,3,0]octane (14).

[0028] 10 g (0.021 mol) enone (13) and 3.1 g (0,008 mol) cerous-chloride heptahydrate in 50 ml methanol and 20 ml CH_2Cl_2 were charged to a 200 ml round bottom flask equipped with a magnetic stirring bar and was cooled to -78 °C under nitrogen. Sodium borohydride was added in small portions, after 30 min the reaction mixture was quenched by addition of saturuted NH_4Cl, and extracted with 2x50 ml ethyl acetate. The extracts were dried and concentrated to leave a colourless oil (98 % yield).

4.3 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo-[3,3,0] octane (15).

[0029] To a solution of 9.8 g (0.02 mol) lactone (14) in 100 ml absolute methanol was added 1.7 (0.012 mol) potassium carbonate. The mixture was stirred with a magnetic bar, at room temperature. After 3 h the mixture was neutralized with 40 ml HCl 1 M, and extracted with 2x50 ml ethyl acetate. The extracts were then dried on unhydrous sodium sulfate and concentrated. The crude product was chromatographed on silica gel using ethyl acetate: acetone as eluent. The title compound (15) was obtained as an oily substance (°5 % yield).

4.4 Preparation of 1-(S)-2-oxa-3-hydroxy-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo[3,3,0] octane (16).

[0030] To a solution of 3g(0.011 mol) lactone (15) in 60 ml unhydrous THF, stirred magnetically and cooled to -78 °C, 4.5 g (0.0315 mol) DIBAL-H in toluene was added dropwise. After 2h the reaction mixture was quenched by addition of 75 ml methanol. The mixture was filtered,the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel-60 using ethyl acetate: acetone 1:1 as eluent. The title compound (16) was obtained as a semisolid substance (78 % yield).

4.5 Preparation of 15-(R,S)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$(17).

[0031] 2.5 g (25 mmol) sodium methyl sulfinylmethide in DMSO (freshly prepared from sodium anhydride and DMSO) was added dropwise to a solution of 5.6 g (12.6 mmol) 4-caboxybutyl triphenyl-phosphonium bromide in 12 ml DMSO. To the resultant red solution of the ylide was added dropwise a solution of the 1.2 g (4.2 mmol) hemiacetal (16) in 13 ml DMSO, and the mixture was stirred for 1h. The reaction mixture was diluted with 10 g ice and 10 ml water and extracted with 2x50 ml ethyl acetate, whereafter the aqueous layer was cooled, acidified with HCl 1 M and extracted with ethyl acetate, and then the organic layer was dried and concentrated. The resulting crude product was a colourless substance. The purity of the title compound (17) was estimated by TLC on silica gel using ethyl acetate: acetone: acetic acid 1:1:0.2 v/v/v as eluent.

4.6 Preparation of 15-(R)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (7).

[0032] The crude product (17) was esterified following a procedure similar to that described in example 2 the product was purified by column chromatography on silica get-60 using ethyl acetate as eluent and the resulting mixture of C_{15} epimeric alcohol were separated.

[0033] The title compound (7) was obtained as a colourless oily substance (46 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H m)	5.4 (2H m)
3.9 (1 H m)	5.6 (2H m)
4.15 (2H m)	7.2 (5H m)
4.95 (1 H m)	

Example 5: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (5).

[0034] Following a procedure similar to that described in example 7, with minor modification, 5 g (0.018 mol) enone (13) in 100 ml THF was reduced using 2.03 g 10 % pd/c under hydrogen atmosphere. After completion of the reaction (as determined by TLC on silica gel using ethylacetate: toluene 1:1 as eluent) the mixture was filtered on celite. The filtrate was concentrated in vacuo and an oily substance was obtained (86 % yield).

[0035] The final product 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester containing a mixture of C_{15} epimeric alcohols were separated by preparative liquid chromatography using 40 % CH_3CN in water v/v as eluent.

Nuclear Magnetic Renonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.0 (1H m)
3.6 (1 H m)	5.4 (2H m)
3.9 (1 H m)	7.2 (5H m)
4.15 (1H m)	

Studies of eye pressure lowering effect and adverse reactions

[0036] The intraocular pressure (IOP) was determined in animals with a pneumatonometer (Digilab Modular One™, Bio Rad), specially calibrated for the eye of the particular species. The cornea was anaesthetized with 1-2 drops of oxibuprocain before each IOP measurement. In healthy human volunteers IOP was measured with applanation tonometry or with an air puff tonometer (Keeler pulsair). For applanation tonometry either a pneumatonometer (Digilab) or Goldmann's applanation tonometer mounted on a slit lamp microscope was used. The cornea was anaesthetized with oxibuprocain before each measurement with applanation tonometry. No local anaesthesia was employed before measurement with the pulsair tonometer.

[0037] The ocular discomfort after application of the test substances was evaluated in cats. The behaviour of cats after topical application of the test drug was followed and ocular discomfort was graded on a scale from 0 to 3, 0 indicating complete absence of any signs of discomfort, and 3 indicating maximal irritation as obvious from complete lid closure.

[0038] Conjunctival hyperemia after topical application of the test substances was evaluated in rabbits. The conjunctiva at the insertion of the superior rectus muscle of the eye was inspected or photographed with regular intervals and the degree of hyperemia was later evaluated from the color photographs in a blind manner. Conjunctival hyperemia was evaluated on a scale from 0 to 4, 0 indicating complete absence of any hyperemia, and 4 indicating marked hyperemia with conjunctival chemosis.

[0039] For determination of the effects on the intraocular pressure, primarily monkeys (cynomolgus) were employed. The reason for this is that the monkey eye is highly reminiscent of the human eye and therefor, generally, drug effects are readily extrapolated to the human eye. However, the disadvantage of using the monkey eye as a model is that the conjunctiva in this species is pigmented making it impossible to evaluate conjunctival hyperemia and furthermore, the monkey eye is relatively insensitive to irritation. Therefore, the cat eye, being very sensitive to prostaglandins was used for evaluating ocular discomfort and the rabbit eye with pronounced tendency to hyperemic reactions was used for evaluating conjunctival and episcleral hyperemia.

[0040] It is evident from Table III that modification of the omega chain of the prostaglandin skeleton introduced new and unexpected features to the prostaglandins with respect to ocular irritation (discomfort). Particularly 17-phenyl,

18,19,20-trinor-$PGF_{2\alpha}$-IE and analogs were unique in exhibiting a complete loss of ocular irritation with retained IOP lowering effect in monkeys. The 17-phenyl,18,19,20-trinor-$PGF_{2\alpha}$ derivatives were extremely well tolerated and 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE, had no or very little irritating effect in the eye of cats. Thus, modifying the omega chain and substituting a carbon atom in the chain with a ring structure introduces completely new, unexpected and advantageous qualities to naturally occuring prostaglandins in that the irritating effect in the conjunctiva and cornea is abolished.

[0041] In addition to the lack of ocular discomfort the omega chain modified analogs also exhibited an advantage over naturally occuring prostalgandins in that they caused considerably less conjunctival hyperemia as studied in the rabbit eye (Table IV). Particularly, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE,13,14-dihydro-17-phenyl-18,19,20-trinor--$PGF_{2\alpha}$-IE, and 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-IE were adventageous in this respect.

[0042] The intraocular pressure lowering effect of omega chain modified and ring-substituted prostaglandin analogs is demonstrated in Table V. It can be seen that 17-phenyl-trinor prostaglandin analogs significantly reduced IOP in animal eyes (Table V). In all but two series of experiments cynomolgus monkeys were used. It is of particular interest to note that 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-derivatives exhibiting no ocular irritation and only modest conjunctival/episcleral hyperemia significantly lowered IOP in primates.

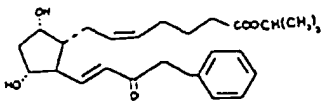
[0043] It is noteworthy that most of the 17-phenyl,18,19,20-trinor-prostaglandin analogs had poor intraocular pressure lowering effect in cats, even at high doses. It is to be observed that the doses at which compounds were used presented in Table III are lower than those e.g. in Table V. Doses presented in Table III should be explicitly compared with those of the naturally occuring prostaglandins in the same table. The same is true for Table IV. It is clear that with increasing dose side effects may increase. However, the doses of prostaglandin derivatives used in monkeys are comparatively similar to those used in human volunteers, (Table VI) being practically free of side effects.

[0044] The effect of some omega chain modified prostaglandin analogs, more specifically 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, and 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, on the intraocular pressure of healthy human volunteers is demonstrated in Table VI. All compounds significantly reduced the intraocular pressure. It is particularly significant in this respect that none of the compounds had any significant irritating effect (ocular discomfort) and that 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE and 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE caused very little if any conjunctival/episcleral hyperemia in man. Thus, omega chain modified, and ring substituted prostaglandin analogs seem to be unique in that these compounds reduce IOP without causing significant ocular side effects such as hyperemia and discomfort.

[0045] The present invention thus describes a group of compounds exhibiting the unique property of causing insignificant ocular side effects while retaining the intraocular pressure lowering effect. From the foregoing it is evident that the crucial modification of the molecule is a ring structure in the omega chain. Furthermore, substituents in the ring structure and/or in the omega chain may be introduced in certain molecules still exhibiting some side-effects in the eye. Hetero atoms may also be introduced into the ring substituted omega chain. Presently, particularly 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-derivatives seem very promising for therapeutic use in glaucoma. From the scientific literature it is evident that PGA_2 or its esters lower IOP in the monkey (see Bito et al, 1989).

[0046] Thus, the analogy with $PGF_{2\alpha}$ and its esters lowering IOP in the primate eye is logic. It is most reasonable to assume that other prostaglandins with modified omega chain exhibit essentially the same properties as $PGF_{2\alpha}$ with modified omega chain, i.e. IOP lowering effect without side effects.

TABLE I.



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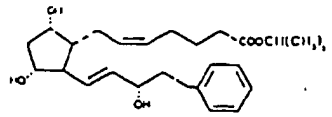

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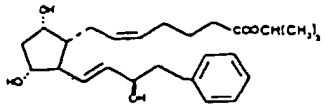

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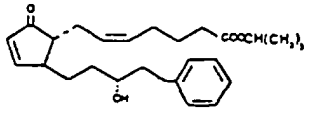

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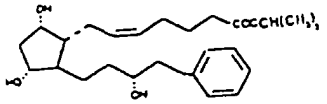

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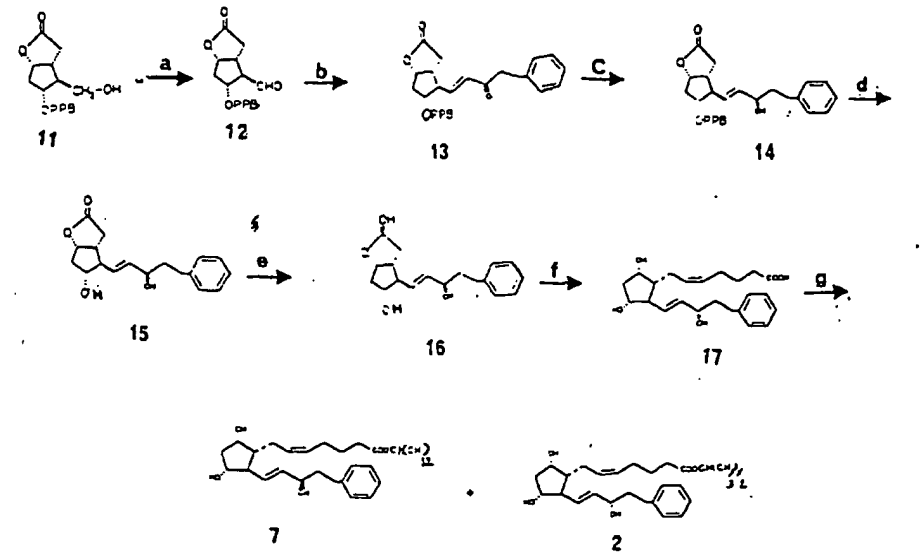
TABLE II.



Reagents:
a) DCC/DMSO/DME
b) NaH/ dimethyl-2-oxo-4-phenylbutyl phosphonate/DME
c) $CeCl_3.7H_2O/NaBH_4$/ CH_3OH/ -78°C
d) K_2CO_3/CH_3OH
e) Dibal/-78°C
f) $NaCH_2SOCH_3$/
(4-carboxybutyl)-triphenylphosphonium bromide/DMSO
g) DBU/IprI/acetone

Table III.

Irritative effect of naturally occuring prostaglandins ($PGF_{2\alpha}$, PGD_2 and PGE_2), and omega chain modified analogs applied as isopropylester on the cat eye. The avarage degree of discomfort was evaluated during 60 min after topical application of the respective test drug. The numbers within paranthesis refer to Table I.

Substance	Dose (pg)	Degree of occular irritation
$PGF_{2\alpha}$-isopropylester (-IE)	1	3.0 ± 0.0
15-propionate-PGE_2-IE	0.1-1	3.0 ± 0.0
15-propionate-PGD_2-IE	1	1.3 ± 0.2
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (1)	1-5	0
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (2)	5	0
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (4)	1-5	0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (5)	1	0

Table III. (continued)

Irritative effect of naturally occuring prostaglandins ($PGF_{2\alpha}$, PGD_2 and PGE_2), and omega chain modified analogs applied as isopropylester on the cat eye. The avarage degree of discomfort was evaluated during 60 min after topical application of the respective test drug. The numbers within paranthesis refer to Table I.		
Substance	**Dose (pg)**	**Degree of occular irritation**
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE (3)	1	0

Table IV.

Degree of conjunctival hyperemia in the rabbit eye after application of naturally occuring prostaglandins ($PGF_{2\alpha}$, and PGE_2), and omega chain modified analogs applied as isopropylesters.		
Substance	**Dose (µg)**	**Degree of hyperemia**
$PGF_{2\alpha}$-isopropylester (-IE)	0.1	2.8 ± 0.2
15-propionate-PGE_2-IE	0.5	2.7 ± 0.3
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (1)	0.5	2.0 ± 0.3
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (2)	0.5	0.7 ± 0.3
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (4)	0.5	2.0 ± 0.0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (5)	0.5	1.3 ± 0.3
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE (3)	0.5	0.3 ± 0.3

Table V. Intraocular pressure reducing effect of naturally occuring prostaglandin ($PGF_{2\alpha}$) and omega chain modified analogs as determined in cynomolgus monkeys or cats. Unless specified data were obtained in monkeys. The figures within parenthesis refer to formulas given in Table I.

* Indicates statistical significance $p < 0.05$. The substances were applied topically.
** Data obtained in cat eyes.

Substance	Dose (µg)	Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)
		E 11.4±0.7	8.3±0.5	8.0±0.6	9.3±0.8
$PGF_{2\alpha}$-isopropylester (IE)	1.5	C 11.0±0.7	10.7±0.4 *	10.1±0.4 *	10.6±0.9
17-phenyl-18,19,20-	3.2	E 12.8±0.6	11.9±0.5	8.6±0.3	9.5±0.7
trinor-$PGF_{2\alpha}$-IE	(1)	C 13.4±0.6	11.7±0.6	12.4±0.2 *	11.9±0.7
13,14-dihydro-17-phenyl-	10.4	E 11.1±0.9	8.3±0.6	6.9±0.4	7.7±0.8
18,19,20-trinor-$PGF_{2\alpha}$-IE	(6)	C 10.6±0.7	8.8±0.9	10.3±1.1 *	9.5±1.0

Table V cont.

Substance	Dose (µg)	Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)

Table VI. Intraocular pressure reducing effect of different omega chain modified and ring substituted $PGF_{2\alpha}$-IE analogs in healthy human volunteers. The substance number is given within parenthesis.

* Indicates statistical significance p <0.05.

Substance	Dose (µg)	n	Eye	Time after administration (hours) 0 (mmHg)	4 (mmHg)	6 (mmHg)	8 (mmHg)
17-phenyl-18,19,20-trinor-	1	4	Exp	11.9±1.7	11.0±0.9	10.1±0.7	9.8±0.7
					*	*	*
$PGF_{2\alpha}$-isopropylester (IE) (1)			Contr	12.7±1.7	13.9±0.7	13.5±1.2	12.5±0.7
15-(R)-17-phenyl-18,19,20-	10	3	Exp	12.9±0.9	11.8±0.6	11.0±0.3	11.2±1.3
							*
trinor-$PGF_{2\alpha}$-IE (4)			Contr	13.2±1.4	13.7±0.9	13.8±1.0	15.1±1.3
15-dehydro-17-phenyl-	10	4	Exp	17.7±0.6	14.6±0.2	13.6±0.7	-
					*	*	
18,19,20-trinor-$PGF_{2\alpha}$-IE (2)			Contr	17.5±0.7	16.4±0.5	16.3±1.0	-
13,14-dihydro-17-phenyl-	1	4	Exp	14.2±0.5	13.3±1.1	12.2±0.4	12.5±0.9
						*	
18,19,20-trinor-$PGF_{2\alpha}$-IE (5)			Contr	13.5±0.6	14.2±1.2	15.2±1.0	15.1±0.7

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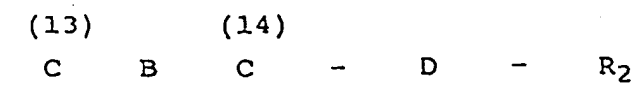
Claims

Claims for the following Contracting States : AT, SE

1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group
R_2 is a

(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a

phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to claim 1 or claim 2 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

4. Use according to anyone of claims 1-3 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

5. Use according to claim 3 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

6. Use according to claim 5 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

7. Use according to claim 6 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA or PGF.

8. Use according to claim 6 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA. or PGF

9. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

10. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

11. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

12. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

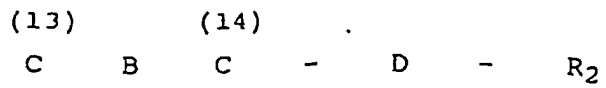
14. Use according to anyone of claims 9 to 13, wherein the ester of the prostaglandin derivative is the isopropylester.

15. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

16. 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

17. 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

18. An ophthalmological composition for topical treatment of glaucoma or ocular hypertension which comprises an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,
R_2 is

(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

in an ophthalmologically compatible carrier.

19. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

20. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

21. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

22. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

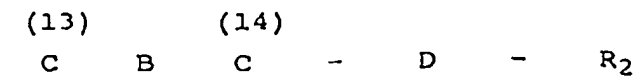
23. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

24. An ophthalmological composition according to anyone of claims 18 to 22 containing 0.1-30 µg of the prostaglandin derivative

25. An ophthalmological composition according to claim 23 containing 1-10 µg of the prostaglandin derivative.

Claims for the following Contracting States : ES, GR

1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group
R_2 is a

(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a phenyl group; or

(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to claim 1 or claim 2 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

4. Use according to anyone of claims 1-3 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

5. Use according to claim 3 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

6. Use according to claim 5 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

7. Use according to claim 6 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA' or PGF.

8. Use according to claim 6 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA or PGF

9. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

10. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

11. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

12. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

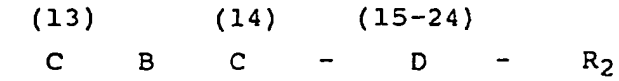
14. Use according to anyone of Claims 9 to 13, wherein the ester of the prostaglandin derivative is the isopropylester.

15. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

16. 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

17. 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

18. Method for producing an ophthalmological composition for topical treatment of glaucoma or ocular hypertension comprising admixing an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,
R_2 is

(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

and an ophthalmologically compatible carrier.

19. Method according to claim 18 wherein the prostaglandin derivative is an ester.

20. Method according to any one of claims 18-19 wherein B is single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

21. Method according to any one of claims 18-20 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

22. Method according to claim 20 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

23. Method according to claim 22 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

24. Method according to claim 22 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative.

25. Method according to claim 19 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

26. Method according to claim 19 wherein the prostaglandin derivative is a 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

27. Method according to claim 19, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_2 α-alkyl ester with 1-10 carbon atoms.

28. Method according to any one of claims 18 to 27 wherein the ester of the prostaglandin derivative is the isopropyl-ester.

29. Method according to anyone of claims 18 to 27 wherein the amount of prostaglandin derivative is 0.1-30 µg.

30. Method according to claim 29 wherein the amount of prostaglandin derivative is 1-10 µg.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, SE

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die Formel

(13) (14)

C B C - D - R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 oder 2, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

5. Verwendung nach Anspruch 3, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

6. Verwendung nach Anspruch 5, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat ist.

7. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat von PGA oder PGF ist.

8. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA oder PGF ist.

9. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

10. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

11. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGA_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

12. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach einem der Ansprüche 9 bis 13, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

15. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

16. 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

17. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester.

18. Ophthalmologisches Präparat zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, umfassend eine wirksame, den Augeninnendruck reduzierende Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die folgende Formel

(13)		(14)				
C	B	C	-	D	-	R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

in einem ophthalmologisch verträglichen Träger.

19. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester ist.

20. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester ist.

21. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester ist.

22. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

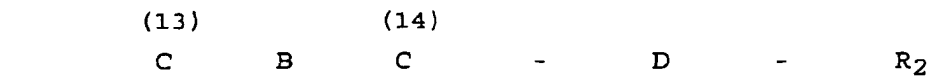
23. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

24. Ophthalmologisches Präparat nach einem der Ansprüche 18 bis 22, umfassend 0,1-30 µg des Prostaglandinderivats.

25. Ophthalmologisches Präparat nach Anspruch 23, umfassend 1-10 µg des Prostaglandinderivats.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die Formel



besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterocyclische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 oder 2, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

5. Verwendung nach Anspruch 3, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

6. Verwendung nach Anspruch 5, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat ist.

7. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat von PGA oder PGF ist.

8. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA oder PGF ist.

9. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

10. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

11. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGA_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

12. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach einem der Ansprüche 9 bis 13, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

15. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

16. 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

17. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester.

18. Verfahren zur Herstellung eines ophthalmologischen Präparats zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, umfassend Mischen einer wirksamen, den Augeninnendruck reduzierenden Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die folgende Formel

(13)		(14)		(15-24)		
C	B	C	-	D	-	R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterocyclische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

mit einem ophthalmologisch verträglichen Träger.

19. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

20. Verfahren nach einem der Ansprüche 18 und 19, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

21. Verfahren nach einem der Ansprüche 18 bis 20, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die substituiert ist oder mindestens einen Substituenten ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

22. Verfahren nach Anspruch 20, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

23. Verfahren nach Anspruch 22, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

24. Verfahren nach Anspruch 22, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat ist.

25. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

26. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

27. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

28. Verfahren nach einem der Ansprüche 18 bis 27, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

29. Verfahren nach einem der Ansprüche 18 bis 27, umfassend 0,1-30 µg des Prostaglandinderivats.

30. Verfahren nach Anspruch 29, umfassend 1-10 µg des Prostaglandinderivats.

Revendications

Revendications pour les Etats contractants suivants : AT, SE

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :

$$\underset{(13)}{C}\quad \underset{}{B}\quad \underset{(14)}{C}\quad -\quad D\quad -\quad R_2$$

dans laquelle
C représente un atome de carbone (le numéro est inscrit entre parenthèses),
B représente une liaison simple, une double liaison ou une triple liaison,
D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,
R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes

nitro, des atomes d'halogènes ou un groupe phényle.

5. Utilisation suivant la revendication 3, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

6. Utilisation suivant la revendication 5, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

7. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA ou PGF.

8. Utilisation suivant la revendication 6, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA ou PGF.

9. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

10. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

11. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2á}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

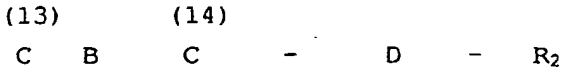
14. Utilisation suivant l'une quelconque des revendications 9 à 13, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

15. Ester isopropylique de 13,14-dihydro-17-phényl-18, 19, 20-trinor-$PGF_{2\alpha}$.

16. Ester isopropylique de 15-déshydro-17-phényl-18, 19, 20-trinor-$PGF_{2\alpha}$.

17. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

18. Composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, qui comprend une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 3 atomes de carbone, interrompue facultativement par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino

aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

dans un véhicule ophtalmologiquement compatible.

19. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

20. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

21. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

22. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

23. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

24. Composition ophtalmologique suivant l'une quelconque des revendications 18 à 22, contenant 0,1 à 30 µg du dérivé de prostaglandine.

25. Composition ophtalmologique suivant la revendication 23, contenant 1 à 10 µg du dérivé de prostaglandine.

Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :

$$\overset{(13)}{C}\quad \overset{}{B}\quad \overset{(14)}{C}\quad -\quad D-\quad R_2$$

dans laquelle
C représente un atome de carbone (le numéro est indiqué entre parenthèses),
B représente une liaison simple, une double liaison ou une triple liaison,
D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,
R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

5. Utilisation suivant la revendication 3, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

6. Utilisation suivant la revendication 5, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

7. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA ou PGF.

8. Utilisation suivant la revendication 6, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA ou PGF.

9. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

10. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

11. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant l'une quelconque des revendications 9 à 13, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

15. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF2α.

16. Ester isopropylique de 15-dihydro-17-phényl-18,19,20-trinor-PGF2α.

17. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

18. Procédé de production d'une composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, comprenant le mélange d'une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :

$$\overset{(13)}{C}\ \overset{}{B}\ \overset{(14)}{C}\ -\ D\ -\ R_2$$

dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

(i) un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et le groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

et un véhicule ophtalmologiquement compatible.

19. Procédé suivant la revendication 18, dans lequel le dérivé de prostaglandine est un ester.

20. Procédé suivant l'une quelconque des revendications 18 et 19, dans lequel B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou bien est substitué avec un groupe (R)-OH ou (S)-OH.

21. Procédé suivant l'une quelconque des revendications 18 à 20, dans lequel R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle.

22. Procédé suivant la revendication 20, dans lequel le dérivé de prostaglandine est le dérivé à fonction 17-phényl-18,19,20-trinor.

23. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est le dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

24. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor.

25. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

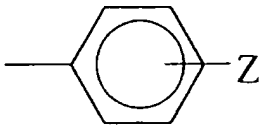
26. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

27. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'α-alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF_2.

28. Procédé suivant l'une quelconque des revendications 18 à 27, dans lequel l'ester du dérivé de prostaglandine est l'ester isopropylique.

29. Procédé suivant l'une quelconque des revendications 18 à 27, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 0,1 à 30 µg.

30. Procédé suivant la revendication 29, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 1 à 10 µg.



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,
in einem ophthalmologisch verträglichen Träger.

28. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

29. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

30. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester ist.

31. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

32. Ophthalmologisches Präparat nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat der 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

33. Ophthalmologisches Präparat nach einem der Ansprüche 27 bis 31, umfassend 0,1-30 µg des Prostaglandinderivats.

34. Ophthalmologisches Präparat nach Anspruch 32, umfassend 1-10 µg des Prostaglandinderivats.

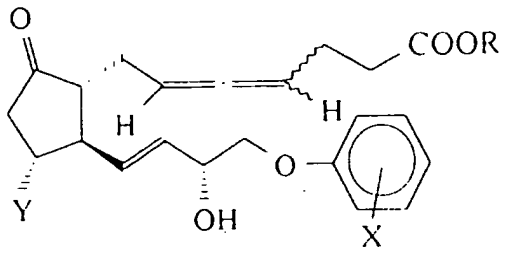
Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die Formel

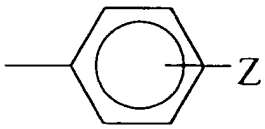
(13)		(14)		(15-24)		
C	B	C	-	D	-	R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,
unter Ausschluß von

- 11-substituierten-16-Phenoxy-PGE-Derivaten der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,
zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 und 2, dadurch **gekennzeichnet,** daß D eine Kette mit 2-8 Kohlenstoffatomen ist.

4. Verwendung nach Anspruch 3, dadurch **gekennzeichnet,** daß D eine Kette mit 2-5 Kohlenstoffatomen ist.

5. Verwendung nach Anspruch 4, dadurch **gekennzeichnet,** daß D eine Kette mit 3 Kohlenstoffatomen ist.

6. Verwendung nach einem der Ansprüche 1 bis 5, dadurch **gekennzeichnet,** daß B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

7. Verwendung nach einem der Ansprüche 1 bis 6, dadurch **gekennzeichnet,** daß R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

8. Verwendung nach Anspruch 6, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

9. Verwendung nach Anspruch 8, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

10. Verwendung nach Anspruch 9, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

11. Verwendung nach Anspruch 9, dadurch **gekennzeichnet,** daß das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA, PGE oder PGF ist.

12. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkylester mit 1-10 Kohlenstoffatomen ist.

15. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

16. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

17. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

18. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-PGE_2-alkylester mit 1-10 Kohlenstoffatomen ist.

19. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

20. Verwendung nach Anspruch 2, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 19-Phenyl-20-nor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

21. Verwendung nach einem der Ansprüche 12 bis 20, dadurch **gekennzeichnet,** daß der Ester des Prostaglandinderivats der Isopropylester ist.

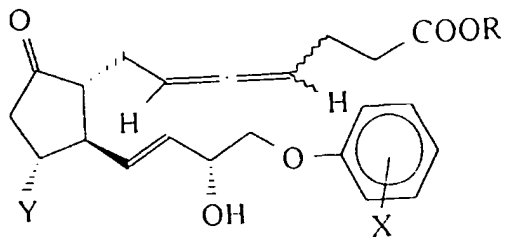
22. Verfahren zur Herstellung eines ophthalmologischen Präparats zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, dadurch **gekennzeichnet,** daß man eine wirksame, den Augeninnendruck reduzierende Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB, PGE oder PGF, worin die Omega-Kette die Formel

$$\underset{(13)}{C}\quad\underset{}{B}\quad\underset{(14)}{C}\quad-\quad\underset{(15\text{-}24)}{D}\quad-\quad R_2$$

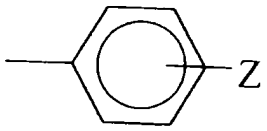
besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 1-10 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2
(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder

(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol, ist,

unter Ausschluß von 11-substituierten-16-Phenoxy-PGE-Derivaten der Formel



worin R Wasserstoff, Niedrigalkyl bedeutet; X Wasserstoff, Halogen, Trifluormethyl, Niedrigalkyl oder Niedrigalkoxy bedeutet; Y Niedrigalkyl bedeutet oder



bedeutet, worin Z Wasserstoff, Halogen, Methyl, Methoxy oder Trifluormethyl bedeutet, und die Wellenlinien die α- oder β-Konfiguration bedeuten, mit der Maßgabe, daß, wenn eine Wellenlinie α bedeutet, die andere β bedeutet,

und einen ophthalmologisch verträglichen Träger miteinander vermischt.

23. Verfahren nach Anspruch 22, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein Ester ist.

24. Verfahren nach einem der Ansprüche 22 und 23, dadurch **gekennzeichnet,** daß D eine Kette mit 2-8 Kohlenstoffatomen ist.

25. Verfahren nach Anspruch 24, dadurch **gekennzeichnet,** daß D eine Kette mit 2-5 Kohlenstoffatomen ist.

26. Verfahren nach Anspruch 25, dadurch **gekennzeichnet,** daß D eine Kette mit 3 Kohlenstoffatomen ist.

27. Verfahren nach einem der Ansprüche 22 bis 26, dadurch **gekennzeichnet,** daß B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

28. Verfahren nach einem der Ansprüche 22 bis 27, dadurch **gekennzeichnet,** daß R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

29. Verfahren nach Anspruch 27, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

30. Verfahren nach Anspruch 29, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

31. Verfahren nach Anspruch 29, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat ist.

32. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

33. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

34. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

35. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 16-Phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

36. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-PGE_2-alkylester mit 1-10 Kohlenstoffatomen ist.

37. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 18-Phenyl-19,20-dinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

38. Verfahren nach Anspruch 23, dadurch **gekennzeichnet,** daß das Prostaglandinderivat ein 19-Phenyl-20-nor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

39. Verfahren nach einem der Ansprüche 22 bis 38, dadurch **gekennzeichnet,** daß der Ester des Prostaglandinderivats der Isopropylester ist.

40. Verfahren nach einem der Ansprüche 22 bis 39, dadurch **gekennzeichnet,** daß die Menge des Prostaglandinderivats 0,1-30 µg beträgt.

41. Verfahren nach Anspruch 40, dadurch **gekennzeichnet,** daß die Menge des Prostaglandinderivats 1-10 µg beträgt.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :

dans laquelle

C représente un atome de carbone (le numéro est inscrit entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

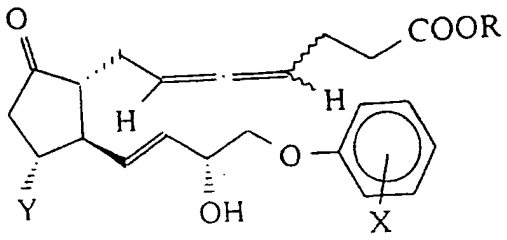
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

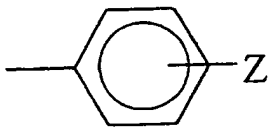
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion des dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans lequel Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant l'une quelconque des revendications 1 et 2, dans laquelle D représente une chaîne ayant 2 à 8 atomes de carbone.

4. Utilisation suivant la revendication 3, dans laquelle D représente une chaîne ayant 2 à 5 atomes de carbone.

5. Utilisation suivant la revendication 4, dans laquelle D représente une chaîne ayant 3 atomes de carbone.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

7. Utilisation suivant l'une quelconque des revendications 1 à 6, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

8. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

9. Utilisation suivant la revendication 8, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

10. Utilisation suivant la revendication 9, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

11. Utilisation suivant la revendication 9, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

15. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

16. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

17. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

18. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

19. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

20. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

21. Utilisation suivant l'une quelconque des revendications 12 à 20, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

22. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

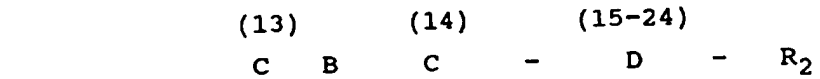
23. Ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

24. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

25. Ester isopropylique de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

26. Ester isopropylique de 19-phényl-20-nor-$PGF_{2\alpha}$.

27. Composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, qui comprend une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 1 à 10 atomes de carbone, interrompue facultativement par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des

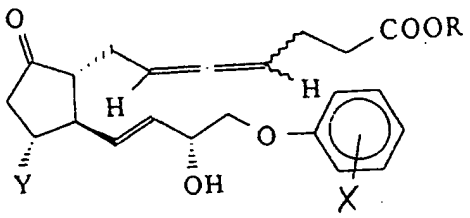
groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

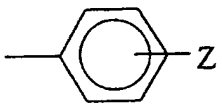
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion des compositions contenant des dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans laquelle Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

dans un véhicule ophtalmologiquement compatible.

28. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

29. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

30. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

31. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

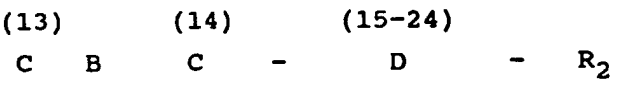
32. Composition ophtalmologique suivant la revendication 27, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

33. Composition ophtalmologique suivant l'une quelconque des revendications 27 à 31, contenant 0,1 à 30 µg du dérivé de prostaglandine.

34. Composition ophtalmologique suivant la revendication 32, contenant 1 à 10 µg du dérivé de prostaglandine.

Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

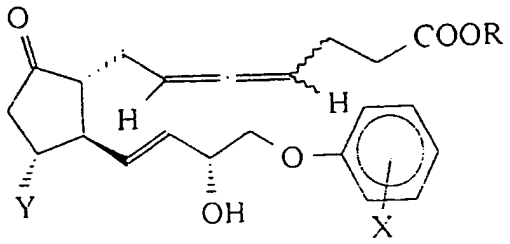
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

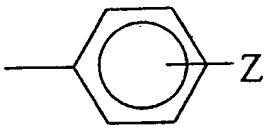
(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion de dérivés de 16-phénoxy-PGE substitués en position 11, répondant à la formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans lequel Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant l'une quelconque des revendications 1 et 2, dans laquelle D représente une chaîne ayant 2 à 8 atomes de carbone.

4. Utilisation suivant la revendication 3, dans laquelle D représente une chaîne ayant 2 à 5 atomes de carbone.

5. Utilisation suivant la revendication 4, dans laquelle D représente une chaîne ayant 3 atomes de carbone.

6. Utilisation suivant l'une quelconque des revendications 1 à 5, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

7. Utilisation suivant l'une quelconque des revendications 1 à 6, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

8. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

9. Utilisation suivant la revendication 8, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

10. Utilisation suivant la revendication 9, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

11. Utilisation suivant la revendication 9, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA, PGE ou PGF.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

15. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

16. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

17. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

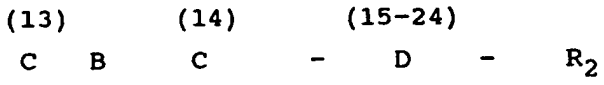
18. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

19. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

20. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

21. Utilisation suivant l'une quelconque des revendications 12 à 20, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

22. Procédé de production d'une composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, comprenant le mélange d'une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB, PGE ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

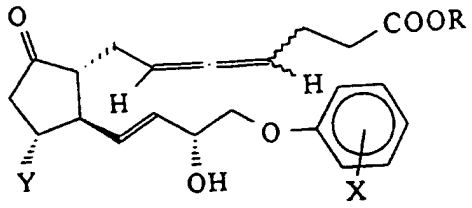
D représente une chaîne ayant 1 à 10 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

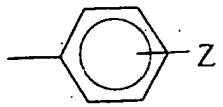
(i) un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et le groupe phényle : ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

à l'exclusion de dérivés de 16-phénoxy-PGE substitués en position 11, de formule



dans laquelle R représente l'hydrogène ou un groupe alkyle inférieur ; X représente l'hydrogène, un groupe halogéno, trifluorométhyle, alkyle inférieur ou alkoxy inférieur ; Y représente un groupe alkyle inférieur ou



dans laquelle Z représente l'hydrogène, un groupe halogéno, méthyle, méthoxy ou trifluorométhyle ; et les lignes ondulées représentent la configuration α ou β, sous réserve que, lorsqu'une ligne ondulée représente la configuration α, l'autre représente la configuration β,

et un véhicule ophtalmologiquement compatible.

23. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est un ester.

24. Procédé suivant l'une quelconque des revendications 22 et 23, dans lequel D représente une chaîne ayant 2 à 8 atomes de carbone.

25. Procédé suivant la revendication 24, dans lequel D représente une chaîne ayant 2 à 5 atomes de carbone.

26. Procédé suivant la revendication 25, dans lequel D représente une chaîne ayant 3 atomes de carbone.

27. Procédé suivant l'une quelconque des revendications 22 à 26, dans lequel B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou bien est substitué avec un groupe (R)-OH ou (S)-OH.

28. Procédé suivant l'une quelconque des revendications 22 à 27, dans lequel R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle.

29. Procédé suivant la revendication 27, dans lequel le dérivé de prostaglandine est le dérivé à fonction 17-phényl-18,19,20-trinor.

30. Procédé suivant la revendication 29, dans lequel le dérivé de prostaglandine est le dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

31. Procédé suivant la revendication 29, dans lequel le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor.

32. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

33. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

34. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'α-alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF_2.

35. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 16-phényl-17,18,19,20-tétranor-$PGF_{2\alpha}$.

36. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-PGE_2.

37. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 18-phényl-19,20-dinor-$PGF_{2\alpha}$.

38. Procédé suivant la revendication 23, dans lequel le dérivé de prostaglandine est l'ester d'alkyle en C_1 à C_{10} de 19-phényl-20-nor-$PGF_{2\alpha}$.

39. Procédé suivant l'une quelconque des revendications 22 à 38, dans lequel l'ester du dérivé de prostaglandine est l'ester isopropylique.

40. Procédé suivant l'une quelconque des revendications 22 à 39, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 0,1 à 30 µg.

41. Procédé suivant la revendication 40, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 1 à 10 µg.

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Note: Bibliography reflects the latest situation

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(54) Prostaglandin derivatives for the treatment of glaucoma or ocular hypertension

Prostaglandinderivate zur Behandlung des grünen Stars oder einer okularen Hypertension

Dérivés de prostaglandine pour traitement du glaucome ou hypertension oculaire

(84) Designated Contracting States:
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- **Woodward D F, Burke J A, Williams L S, et al. 1989. "Prostaglandin F2a effects on intraocular pressure negatively correlate with FP receptor stimulation. Invest. ophtalmol & vis sci 30(2): 1838-1842**
- **Drugs of the future, 1992, 17(8), pp. 691-704**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 364 417 B9

Description

[0001] The invention is concerned with the use of prostaglandin derivatives of PGA, PGB, and PGF, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension. The invention relates also to ophthalmic compositions, containing an active amount of these prostaglandin derivatives, and the manufacture of such compositions.

[0002] Glaucoma is an eye disorder characterized by increased intraocular pressure, excavation of the optic nerve head and gradual loss of the visual field. An abnormally high intraocular pressure is commonly known to be detrimental to the eye, and there are clear indications that, in glaucoma patients, this probably is the most important factor causing degenerative changes in the retina. The pathophysiological mechanism of open angle glaucoma is, however, still unknown. Unless treated successfully glaucoma will lead to blindness sooner or later, its course towards that stage is typically slow with progressive loss of the vision.

[0003] The intraocular pressure, IOP (abbr. of intraocular pressure) can be defined as according to the formula:

$$IOP = P_e + F \times R \quad (1)$$

where P_e is the episcleral venous pressure, generally regarded as being around 9 mm Hg, F the flow of aqueous humor, and R the resistance to outflow of aqueous humor through the trabecular meshwork and adjacent tissue into Schlemm's canal.

[0004] Besides passing through Schlemm's, canal aqueous humor might also pass through the ciliary muscle into the suprachoroidal space and finally leave the eye through sclera. This uveoscleral route has been described for instance by Bill (1975). The pressure gradient in this case is insignificant compared to the gradient over the interior wall of Schlemm's canal and adjacent tissue in the former case. The flow limiting step along the uveoscleral route is assumed to be the flow from the anterior chamber into the suprachoroidal space.

[0005] A more complete formula is given by:

$$IOP = P_e + (F_t - F_u) \times R \quad (2)$$

where P_e and R are defined as above, F_t is the total outflow of aqueous humor and F_u is the fraction passing via the uveoscleral route.

[0006] IOP in human beings is normally in the range of 12 - 22 mm Hg. At higher values, for instance over 22 mm Hg, there is a risk that the eye may be affected. In one particular form of glaucoma, low tension glaucoma, damage may occur at intraocular pressure levels otherwise regarded as physiologically normal. The reason for this could be that the eye in these individuals is unusually sensitive to pressure. The opposite situation is also known, that some individuals may exhibit an abnormally high intraocular pressure without any manifest defects in the visual field or optic nerve head. Such conditions are usually referred to as ocular hypertension.

[0007] Glaucoma treatments can be given by means of drugs, laser or surgery. In drug treatment, the purpose is to lower either the flow (F) or the resistance (R) which, according to formula (1) above, will result in a reduced IOP; alternatively to increase the flow via the uveoscleral route which according to formula (2) also gives a reduced pressure. Cholinergic agonists, for instance pilocarpine, reduce the intraocular pressure mainly by increasing the outflow through Schlemm's canal.

[0008] Prostaglandins, which recently have met an increasing interest as IOP-lowering substances may be active in that they will cause an increase in the uveoscleral outflow (Crawford et al, 1987, and Nilsson et al, 1987). They do not appear, however to have any effect on the formation of aqueous humor or on the conventional outflow through Schlemm's canal (Crawford et al, 1987).

[0009] The use of prostaglandins and their derivatives is described for instance in US 4599353 and EP 87103714.9, and by Bito LZ et al (1983), Camras CB et al (1981, 1987a, 1987b, 1988), Giuffrè G (1985), Kaufman PL (1986), Kersetter JR et al (1988), Lee P-Y et al (1988) and VillumsenJ et al (1989).

[0010] Certain 11-substituted-16-phenoxy prostaglandin compounds of the PGE type have been disclosed in EP 170258, prostaglandin D_2 derivatives are disclosed in EP 253094, and 13,14-dihydro-15-keto prostaglandins, esp 20-alkyl substitued derivatives, are disclosed in EP 308135.

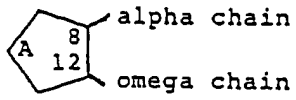
[0011] Woodward et al (1988 and 1989) concluded that studies on cat IOP revealed a substantial decrease for $PGF_{2\alpha}$ whereas identical doses of 16-phenoxy-17,18,19,20-tetranor-$PGF_{2\alpha}$ and 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ were inactive.

[0012] It must be noticed however that even for substances which have been found to lower the intraocular pressure,

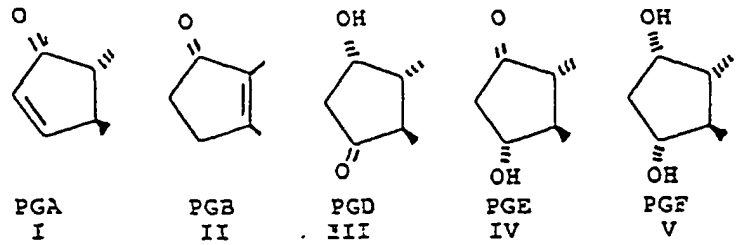
that with respect to the practical usefulness of some of the previously described potentially useful prostaglandins and derivatives, as suitable drugs for treating glaucoma or ocular hypertension, a limiting factor is their property of causing superficial irritation and vasodilation in the conjunctiva. It is probable, moreover, that prostaglandins have an irritant effect on the sensory nerves of the cornea. Thus local side effects will arise in the eye already when the amounts of prostaglandin administered are quite small-that is, already when the doses are lower than those that would be desirable for achieving maximum pressure reduction. It has thus been found, for instance, that for this reason it is clinically impossible to use $PGF_{2\alpha}$-1-isopropyl ester in the amount that would give maximum pressure reduction. Prostaglandins, being naturally occurring autacoids, are very potent pharmacologically and affect both sensory nerves and smooth muscle of the blood vessels. Since the effects caused by administrations of $PGF_{2\alpha}$ and its esters to the eye, comprise in addition to pressure reduction also irritation and hyperemia (increased blood flow), the doses currently practicable in clinical tests are necessarily very low. The irritation experienced when $PGF_{2\alpha}$ or its esters are applied, consists mainly in a feeling of grittiness or of having a foreign body in one's eye, this being usually accompanied by increased lacrimation.

[0013] We have now found that a solution to the problems discussed above is the use of certain derivatives of prostaglandins A, B, and F, in which the omega chain has been modified with the common feature of containing a ring structure, for the treatment of glaucoma or ocular hypertension.

[0014] The prostaglandin derivatives have the general structure



wherein A represents the alicyclic ring C_8-C_{12} and the bonds between the ring and the side chains represent the various isomers. In PGA, PGB, PGD, PGE and PGF A has the formula



The invention is based on the use of derivatives characterized by their omega chain and various modifications of the alpha chain is therefore possible still using the inventive concept. The alpha chain could typically be the naturally occuring alpha chain, which is esterified to the structure

in which R_1 is an alkyl group, preferably with 1-10 carbon, especially 1-6 atoms, for instance metyl, ethyl, propyl, isopropyl, butyl, isobutyl, neopentyl or benzyl or a derivative giving the final substance equivalent properties as a glaucoma agent. The chain could preferably be a C_6-C_{10} chain which might be saturated or unsaturated having one or more double bonds, and allenes, or a triple bond and the chain might contain one or more substituents such as alkyl groups, alicyclic rings, or aromatic rings with or without hetero atoms.

[0015] The omega chain is defined by the following formula:

(13) (14)
C B C - D - R_2

wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by preferably not more than two hetero atoms (O,S, or N), the substituent on each carbon atom being H, alkyl groups, preferably lower alkyl groups within 1-5 carbon atoms, a carbonyl group, or a hydroxyl group, whereby the substituent on C_{15} preferably being a carbonyl group, or (R)-OH or (S)-OH; each chain D containing preferably not more than three hydroxyl groups or not more than three carbonyl groups,
R_2 is a ring structure such as a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole

[0016] Some examples on derivatives which were evaluated are the following (for structure information see Table I):

(1) 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(2) 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(3) 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester
(4) 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester
(5) 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

The most preferred derivatives at present are the 17-phenyl analogs, such as the 15-(R)-, 15-dehydro and 13,14-dihydro-17-phenyl-18,19,20-trinor forms. Such derivatives are represented by (2), (3), (4) and (5) in the formulas given in Table I.

[0017] In the formula given above the most preferred structure at present is accordingly obtained when the prostaglandin is a derivative of PGA or PGF, especially of PGA_2 and $PGF_{2\alpha}$
B is a single bond or a double bond
D is a carbon chain with 3 atoms; C_{15} having a carbonyl or (S)-OH substituent and C_{16}-C_{17} having lower alkyl substituents, or preferably H
R_2 is a phenyl ring optionally having substituents selected among alkyl and alkoxy groups.

[0018] The invention thus relates to the use of certain derivatives of PGA, PGB and PGF for the treatment of glaucoma or ocular hypertension. Among these derivatives defined above it has been found that some are irritating or otherwise not optimal, and in certain cases not even useful due to adverse effects and these are excluded in that the group of prostaglandin derivatives defined above is limited to therapeutically effective and physiologically acceptable derivatives. So is for instance (1) 16-phenyl-17,18,19,20-tetranor-$PGF_{2\alpha}$-isopropyl ester irritating while this can be eliminated by substituting the phenyl ring with a methoxy group giving formula (8) which represents a therapeutically more useful compound, The method for treating glaucoma or ocular hypertension consists in contacting an effective intraocular pressure reducing amount of a composition, as aforesaid, with the eye in order to reduce the eye pessure and to maintain said pressure on a reduced level. The composition contains 0.1-30 µg, especially 1-10 µg, per application of the active substance i.e. a therapeutically active and physiologically acceptable derivative from the group defined above; the treatment may advantageously be carried out in that one drop of the composition, corresponding to about 30 µl, is administered about 1 to 2 times per day to the patient's eye. This therapy is applicable both to human beings and to animals.

[0019] The invention further relates to the use of therapeutically active and physiologically acceptable prostaglandin derivatives from the group defined above for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

The prostaglandin derivative is mixed with an ophthalmologically compatible vehicle known per se. The vehicle which may be employed for preparing compositions of this invention comprises aqueous solutions as e.g. physiological salines, oil solutions or ointments. The vehicle furthermore may contain ophthalmologically compatible preservatives such as e.g. benzalkonium chloride, surfactants like e.g. polysorbate 80, liposomes or polymers, for example methyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone and hyaluronic acid; these may be used for increasing the viscosity. Furthermore, it is also possible to use soluble or insoluble drug inserts when the drug is to be administered.

[0020] The invention is also related to ophthalmological compositions for topical treatment of glaucoma or ocular hypertension which comprise an effective intra ocular pressure reducing amount of a prostaglandin derivative as defined above and an ophthalmologically compatible carrier, the effective amount comprising a dose of about 0.1-30 µ in about

10-50 µ of the composition.

[0021] In the experiments carried out in this investigation the active compound, in an amount, varying with potency of the drug, from 30 µg to 300 µg/ml was dissolved in a sterilized aqueous solution (saline 0.9 %) containing 0.5 % polysorbate-80 as solubilizing agent.

[0022] The invention is illustrated by means of the following non-limitative examples.

Synthesis of prostaglandin derivatives

Example 1: Preparation of 17-phenyl-18,19,20- trinor $PGF_{2\alpha}$-isopropyl ester (1).

[0023] A 50 ml round bottom flask equipped with a magnetic stirring bar was charged whith 20 mg (0.05 mmol) 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$ (Cayman Chemicals), 6 ml acetone, 39.2 mg (0.25 mmol) DBU and 42.5 mg (0.25 mmol) isopropyl iodide. The solution was allowed to stand at room temperature for 24 h, the solvent was removed in vacuo and the residue was diluted with 30 ml of ethyl acetate, washed twice with 10 ml 5 % sodiumhydrogen carbonate and 10 ml 3 % citric acid. The solvent was removed in vacuo, and the crude product was chromatographed on silica gel-60 using ethyl acetate: acetone 2:1 as eluent. The title compound (2) was obtained as an oily substance (65 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	4.9 (1 H m)
3.9 (1 H m)	5.4-5.6 (4H m)
4.1 (1 H t)	7.1-7.3 (5H m)
4.2 (1 H m)	

Example 2: Preparation of 15-dehydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (2)

[0024] 20.9 mg (0.092 mmol) DDQ was added to a solution of 10 mg (0.023 mmol) 17-phenyl-18,19,20 trinor $PGF_{2\alpha}$-isopropyl ester (2) in 8 ml dioxane. The reaction mixture immediately turned brown, the reaction mixture was stirred at room temperature for 24 h. The precipitate formed was filtered, washed with 10 ml ethyl acetate, the filtrate was diluted with 10 ml ethylacetate washed with 2x10 ml water, 2x10 ml NaOH IM and 20 ml brine. The organic layer was dried on unhydrous sodium sulfate and the solvent was removed in vacuo, the residue was purified by column chromatography on silica gel using ethyl acetate: ether 1:1 as eluent. The title compound (3) was obtained as a colourless oily substance (76 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.0 (1H m)	6.2 (1 H d)
4.2 (1H m)	6.7 (1H q)
5.0 (1 H m)	7.1-7.3 (5H m)

Example 3: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-isopropyl ester (3).

[0025] Following a procedure similar to that described in example 2 using 10 mg (0.026 mmol) 13,14-dihydro-17-phenyl PGA_2 (Cayman Chemicals). The crude product was chromatographed on silica gel-60 using ether as eluent. The title compound (6) was an oily substance (48 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.4 (2H m)
4.3 (1 H m)	7.3 (5H m)
5.0 (1 H m)	

Example 4: Preparation of 15-(R)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (4). (Table II)

4.1 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-(3-oxo-5-phenyl-1-trans-pentenyl)-7-(R)-(4-phenylbenzoyloxy)-cis-bicyclo [3,3,0] octane (13).

[0026] 18 g (0.05 mol) alcohol (11), 32 g (0.15 mol) DCC, 39.1 g (0.5 mol) DMSO (newly distilled from CaH_2) and 30 ml DME were charged to a 200 ml flask under nitrogen. Orthophosphoric acid was added in one portion, and an exothermic reaction occured. The reaction mixture was stirred mechanically at room temperature for 2h, and the resultant precipitate was filtered and washed with DME. The filtrate (12) can be used directly for Emmon condensation reaction.

[0027] To a suspension of 1.2 g (0.04 mol) NaH (80 % washed with n-pentane to remove mineral oil) in 100 ml DME under nitrogen was added dropwise 12.3 g (0.048 mol) dimethyl-2-oxo-4-phenylbutyl-phosphonate in 30 ml DME. The mixture was stirred mechanically for 1h at room temperature, then cooled to -10 °C and a solution of the crude aldehyde (12) was added in dropwise. After 15 min at 0 °C and 1h at room temperature the reaction mixture was neutralized with glacial acetic acid, the solvent was removed under vacuum, and to the residue was added 100 ml ethyl acetate, washed with 50 ml water and 50 ml brine. The organic layer was dried over unhydrous sodium sulfate. The solvent was removed in vacuo
and the resulting white precipitate filtered and washed with cold ether. The title compound (13) was obtained as a crystalline substance mp 134.5-135.5 (53 % yield).

4.2 Preparation of 1-(S)-2-oxa-3oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-(4-phenylbenzoyloxy) cis-bicyclo [3,3,0]octane (14).

[0028] 10 g (0.021 mol) enone (13) and 3.1 g (0,008 mol) cerous-chloride heptahydrate in 50 ml methanol and 20 ml CH_2Cl_2 were charged to a 200 ml round bottom flask equipped with a magnetic stirring bar and was cooled to -78 °C under nitrogen. Sodium borohydride was added in small portions, after 30 min the reaction mixture was quenched by addition of saturuted NH_4Cl, and extracted with 2x50 ml ethyl acetate. The extracts were dried and concentrated to leave a colourless oil (98 % yield).

4.3 Preparation of 1-(S)-2-oxa-3-oxo-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo-[3,3,0] octane (15).

[0029] To a solution of 9.8 g (0.02 mol) lactone (14) in 100 ml absolute methanol was added 1.7 (0.012 mol) potassium carbonate. The mixture was stirred with a magnetic bar, at room temperature. After 3 h the mixture was neutralized with 40 ml HCl 1 M, and extracted with 2x50 ml ethyl acetate. The extracts were then dried on unhydrous sodium sulfate and concentrated. The crude product was chromatographed on silica gel using ethyl acetate: acetone as eluent. The title compound (15) was obtained as an oily substance (°5 % yield).

4.4 Preparation of 1-(S)-2-oxa-3-hydroxy-6-(R)-[3-(R,S)-hydroxy-5-phenyl-1-trans-pentenyl]-7-(R)-hydroxy-cis-bicyclo[3,3,0] octane (16).

[0030] To a solution of 3g(0.011 mol) lactone (15) in 60 ml unhydrous THF, stirred magnetically and cooled to -78 °C, 4.5 g (0.0315 mol) DIBAL-H in toluene was added dropwise. After 2h the reaction mixture was quenched by addition of 75 ml methanol. The mixture was filtered,the filtrate was concentrated in vacuo and the residue was chromatographed on silica gel-60 using ethyl acetate: acetone 1:1 as eluent. The title compound (16) was obtained as a semisolid substance (78 % yield).

4.5 Preparation of 15-(R,S)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$(17).

[0031] 2.5 g (25 mmol) sodium methyl sulfinylmethide in DMSO (freshly prepared from sodium anhydride and DMSO) was added dropwise to a solution of 5.6 g (12.6 mmol) 4-caboxybutyl triphenyl-phosphonium bromide in 12 ml DMSO. To the resultant red solution of the ylide was added dropwise a solution of the 1.2 g (4.2 mmol) hemiacetal (16) in 13 ml DMSO, and the mixture was stirred for 1h. The reaction mixture was diluted with 10 g ice and 10 ml water and extracted with 2x50 ml ethyl acetate, whereafter the aqueous layer was cooled, acidified with HCl 1 M and extracted with ethyl acetate, and then the organic layer was dried and concentrated. The resulting crude product was a colourless substance. The purity of the title compound (17) was estimated by TLC on silica gel using ethyl acetate: acetone: acetic acid 1:1:0.2 v/v/v as eluent.

4.6 Preparation of 15-(R)-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (7).

[0032] The crude product (17) was esterified following a procedure similar to that described in example 2 the product was purified by column chromatography on silica get-60 using ethyl acetate as eluent and the resulting mixture of C_{15} epimeric alcohol were separated.

[0033] The title compound (7) was obtained as a colourless oily substance (46 % yield).

Nuclear Magnetic Resonance spectrum ($CDCl_3$),- ppm: δ	
1.2 (6H m)	5.4 (2H m)
3.9 (1 H m)	5.6 (2H m)
4.15 (2H m)	7.2 (5H m)
4.95 (1 H m)	

Example 5: Preparation of 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester (5).

[0034] Following a procedure similar to that described in example 7, with minor modification, 5 g (0.018 mol) enone (13) in 100 ml THF was reduced using 2.03 g 10 % pd/c under hydrogen atmosphere. After completion of the reaction (as determined by TLC on silica gel using ethylacetate: toluene 1:1 as eluent) the mixture was filtered on celite. The filtrate was concentrated in vacuo and an oily substance was obtained (86 % yield).

[0035] The final product 13,14-dihydro-17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-isopropyl ester containing a mixture of C_{15} epimeric alcohols were separated by preparative liquid chromatography using 40 % CH_3CN in water v/v as eluent.

Nuclear Magnetic Renonance spectrum ($CDCl_3$)- ppm: δ	
1.2 (6H d)	5.0 (1H m)
3.6 (1 H m)	5.4 (2H m)
3.9 (1 H m)	7.2 (5H m)
4.15 (1H m)	

Studies of eye pressure lowering effect and adverse reactions

[0036] The intraocular pressure (IOP) was determined in animals with a pneumatonometer (Digilab Modular One™, Bio Rad), specially calibrated for the eye of the particular species. The cornea was anaesthetized with 1-2 drops of oxibuprocain before each IOP measurement. In healthy human volunteers IOP was measured with applanation tonometry or with an air puff tonometer (Keeler pulsair). For applanation tonometry either a pneumatonometer (Digilab) or Goldmann's applanation tonometer mounted on a slit lamp microscope was used. The cornea was anaesthetized with oxibuprocain before each measurement with applanation tonometry. No local anaesthesia was employed before measurement with the pulsair tonometer.

[0037] The ocular discomfort after application of the test substances was evaluated in cats. The behaviour of cats after topical application of the test drug was followed and ocular discomfort was graded on a scale from 0 to 3, 0 indicating complete absence of any signs of discomfort, and 3 indicating maximal irritation as obvious from complete lid closure.

[0038] Conjunctival hyperemia after topical application of the test substances was evaluated in rabbits. The conjunctiva at the insertion of the superior rectus muscle of the eye was inspected or photographed with regular intervals and the degree of hyperemia was later evaluated from the color photographs in a blind manner. Conjunctival hyperemia was evaluated on a scale from 0 to 4, 0 indicating complete absence of any hyperemia, and 4 indicating marked hyperemia with conjunctival chemosis.

[0039] For determination of the effects on the intraocular pressure, primarily monkeys (cynomolgus) were employed. The reason for this is that the monkey eye is highly reminiscent of the human eye and therefor, generally, drug effects are readily extrapolated to the human eye. However, the disadvantage of using the monkey eye as a model is that the conjunctiva in this species is pigmented making it impossible to evaluate conjunctival hyperemia and furthermore, the monkey eye is relatively insensitive to irritation. Therefore, the cat eye, being very sensitive to prostaglandins was used for evaluating ocular discomfort and the rabbit eye with pronounced tendency to hyperemic reactions was used for evaluating conjunctival and episcleral hyperemia.

[0040] It is evident from Table III that modification of the omega chain of the prostaglandin skeleton introduced new and unexpected features to the prostaglandins with respect to ocular irritation (discomfort). Particularly 17-phenyl,

18,19,20-trinor-$PGF_{2\alpha}$-IE and analogs were unique in exhibiting a complete loss of ocular irritation with retained IOP lowering effect in monkeys. The 17-phenyl,18,19,20-trinor-$PGF_{2\alpha}$ derivatives were extremely well tolerated and 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE, had no or very little irritating effect in the eye of cats. Thus, modifying the omega chain and substituting a carbon atom in the chain with a ring structure introduces completely new, unexpected and advantageous qualities to naturally occuring prostaglandins in that the irritating effect in the conjunctiva and cornea is abolished.

[0041] In addition to the lack of ocular discomfort the omega chain modified analogs also exhibited an advantage over naturally occuring prostalgandins in that they caused considerably less conjunctival hyperemia as studied in the rabbit eye (Table IV). Particularly, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE,13,14-dihydro-17-phenyl-18,19,20-trinor--$PGF_{2\alpha}$-IE, and 13,14-dihydro-17-phenyl-18,19,20-trinor PGA_2-IE were adventageous in this respect.

[0042] The intraocular pressure lowering effect of omega chain modified and ring-substituted prostaglandin analogs is demonstrated in Table V. It can be seen that 17-phenyl-trinor prostaglandin analogs significantly reduced IOP in animal eyes (Table V). In all but two series of experiments cynomolgus monkeys were used. It is of particular interest to note that 17-phenyl-18,19,20-trinor $PGF_{2\alpha}$-derivatives exhibiting no ocular irritation and only modest conjunctival/episcleral hyperemia significantly lowered IOP in primates.

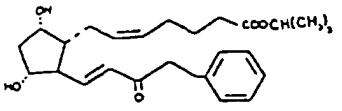
[0043] It is noteworthy that most of the 17-phenyl,18,19,20-trinor-prostaglandin analogs had poor intraocular pressure lowering effect in cats, even at high doses. It is to be observed that the doses at which compounds were used presented in Table III are lower than those e.g. in Table V. Doses presented in Table III should be explicitly compared with those of the naturally occuring prostaglandins in the same table. The same is true for Table IV. It is clear that with increasing dose side effects may increase. However, the doses of prostaglandin derivatives used in monkeys are comparatively similar to those used in human volunteers, (Table VI) being practically free of side effects.

[0044] The effect of some omega chain modified prostaglandin analogs, more specifically 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, and 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE, on the intraocular pressure of healthy human volunteers is demonstrated in Table VI. All compounds significantly reduced the intraocular pressure. It is particularly significant in this respect that none of the compounds had any significant irritating effect (ocular discomfort) and that 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE and 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE caused very little if any conjunctival/episcleral hyperemia in man. Thus, omega chain modified, and ring substituted prostaglandin analogs seem to be unique in that these compounds reduce IOP without causing significant ocular side effects such as hyperemia and discomfort.

[0045] The present invention thus describes a group of compounds exhibiting the unique property of causing insignificant ocular side effects while retaining the intraocular pressure lowering effect. From the foregoing it is evident that the crucial modification of the molecule is a ring structure in the omega chain. Furthermore, substituents in the ring structure and/or in the omega chain may be introduced in certain molecules still exhibiting some side-effects in the eye. Hetero atoms may also be introduced into the ring substituted omega chain. Presently, particularly 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-derivatives seem very promising for therapeutic use in glaucoma. From the scientific literature it is evident that PGA_2 or its esters lower IOP in the monkey (see Bito et al, 1989).

[0046] Thus, the analogy with $PGF_{2\alpha}$ and its esters lowering IOP in the primate eye is logic. It is most reasonable to assume that other prostaglandins with modified omega chain exhibit essentially the same properties as $PGF_{2\alpha}$ with modified omega chain, i.e. IOP lowering effect without side effects.

TABLE I.



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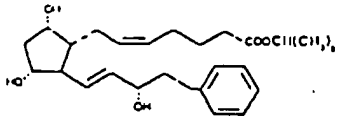

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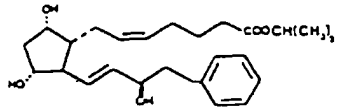

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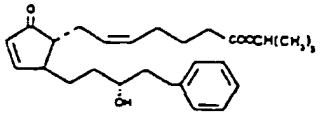

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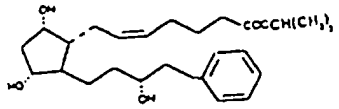

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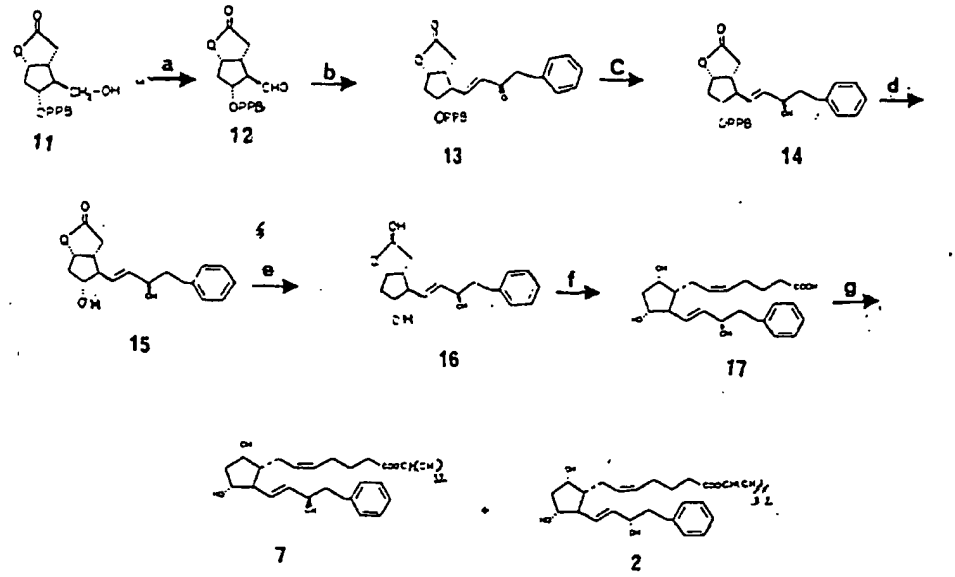
TABLE II.



Reagents:
a) DCC/DMSO/DME
b) NaH/ dimethyl-2-oxo-4-phenylbutyl phosphonate/DME
c) $CeCl_3.7H_2O/NaBH_4$/ CH_3OH/ -78°C
d) K_2CO_3/CH_3OH
e) Dibal/-78°C
f) $NaCH_2SOCH_3$/
(4-carboxybutyl)-triphenylphosphonium bromide/DMSO
g) DBU/IprI/acetone

Table III.

Irritative effect of naturally occuring prostaglandins ($PGF_{2\alpha}$, PGD_2 and PGE_2), and omega chain modified analogs applied as isopropylester on the cat eye. The avarage degree of discomfort was evaluated during 60 min after topical application of the respective test drug. The numbers within paranthesis refer to Table I.

Substance	Dose (pg)	Degree of occular irritation
$PGF_{2\alpha}$-isopropylester (-IE)	1	3.0 ± 0.0
15-propionate-PGE_2-IE	0.1-1	3.0 ± 0.0
15-propionate-PGD_2-IE	1	1.3 ± 0.2
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (1)	1-5	0
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (2)	5	0
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (4)	1-5	0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (5)	1	0

Table III. (continued)

Irritative effect of naturally occuring prostaglandins ($PGF_{2\alpha}$, PGD_2 and PGE_2), and omega chain modified analogs applied as isopropylester on the cat eye. The avarage degree of discomfort was evaluated during 60 min after topical application of the respective test drug. The numbers within paranthesis refer to Table I.		
Substance	**Dose (pg)**	**Degree of occular irritation**
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE (3)	1	0

Table IV.

Degree of conjunctival hyperemia in the rabbit eye after application of naturally occuring prostaglandins ($PGF_{2\alpha}$, and PGE_2), and omega chain modified analogs applied as isopropylesters.		
Substance	**Dose (µg)**	**Degree of hyperemia**
$PGF_{2\alpha}$-isopropylester (-IE)	0.1	2.8 ± 0.2
15-propionate-PGE_2-IE	0.5	2.7 ± 0.3
17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (1)	0.5	2.0 ± 0.3
15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (2)	0.5	0.7 ± 0.3
15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (4)	0.5	2.0 ± 0.0
13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-IE (5)	0.5	1.3 ± 0.3
13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-IE (3)	0.5	0.3 ± 0.3

Table V. Intraocular pressure reducing effect of naturally occuring prostaglandin ($PGF_{2\alpha}$) and omega chain modified analogs as determined in cynomolgus monkeys or cats. Unless specified data were obtained in monkeys. The figures within parenthesis refer to formulas given in Table I.

* Indicates statistical significance $p < 0.05$. The substances were applied topically.
** Data obtained in cat eyes.

Substance	Dose (µg)	Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)
		E 11.4±0.7	8.3±0.5	8.0±0.6	9.3±0.8
			*	*	
$PGF_{2\alpha}$-isopropylester (IE)	1.5	C 11.0±0.7	10.7±0.4	10.1±0.4	10.6±0.9
17-phenyl-18,19,20-	3.2	E 12.8±0.6	11.9±0.5	8.6±0.3	9.5±0.7
				*	
trinor-$PGF_{2\alpha}$-IE	(1)	C 13.4±0.6	11.7±0.6	12.4±0.2	11.9±0.7
13,14-dihydro-17-phenyl-	10.4	E 11.1±0.9	8.3±0.6	6.9±0.4	7.7±0.8
				*	
18,19,20-trinor-$PGF_{2\alpha}$-IE	(6)	C 10.6±0.7	8.8±0.9	10.3±1.1	9.5±1.0

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Table V cont.

Substance	Dose (µg)	Time after administration (hours) 0 (mmHg)	1-2 (mmHg)	3-4 (mmHg)	6 (mmHg)

Table VI. Intraocular pressure reducing effect of different omega chain modified and ring substituted $PGF_{2\alpha}$-IE analogs in healthy human volunteers. The substance number is given within parenthesis.

* Indicates statistical significance p <0.05.

Substance	Dose (µg)	n	Eye	Time after administration (hours)			
				0 (mmHg)	4 (mmHg)	6 (mmHg)	8 (mmHg)
17-phenyl-18,19,20-trinor-	1	4	Exp	11.9±1.7	11.0±0.9 *	10.1±0.7 *	9.8±0.7 *
$PGF_{2\alpha}$-isopropylester (IE) (1)			Contr	12.7±1.7	13.9±0.7	13.5±1.2	12.5±0.7
15-(R)-17-phenyl-18,19,20-	10	3	Exp	12.9±0.9	11.8±0.6	11.0±0.3	11.2±1.3 *
trinor-$PGF_{2\alpha}$-IE (4)			Contr	13.2±1.4	13.7±0.9	13.8±1.0	15.1±1.3
15-dehydro-17-phenyl-	10	4	Exp	17.7±0.6	14.6±0.2 *	13.6±0.7 *	-
18,19,20-trinor-$PGF_{2\alpha}$-IE (2)			Contr	17.5±0.7	16.4±0.5	16.3±1.0	-
13,14-dihydro-17-phenyl-	1	4	Exp	14.2±0.5	13.3±1.1	12.2±0.4 *	12.5±0.9
18,19,20-trinor-$PGF_{2\alpha}$-IE (5)			Contr	13.5±0.6	14.2±1.2	15.2±1.0	15.1±0.7

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Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:

wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group
R_2 is a

(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a

phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to claim 1 or claim 2 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

4. Use according to anyone of claims 1-3 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

5. Use according to claim 3 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

6. Use according to claim 5 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

7. Use according to claim 6 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA or PGF.

8. Use according to claim 6 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA. or PGF

9. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

10. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

11. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

12. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

14. Use according to anyone of claims 9 to 13, wherein the ester of the prostaglandin derivative is the isopropylester.

15. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

16. 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

17. 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

18. An ophthalmological composition for topical treatment of glaucoma or ocular hypertension which comprises an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:

(13) (14)

C B C - D - R_2

wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,
R_2 is

(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

in an ophthalmologically compatible carrier.

19. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

20. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

21. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

22. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

23. An ophthalmological composition according to claim 18 in which the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester.

24. An ophthalmological composition according to anyone of claims 18 to 22 containing 0.1-30 µg of the prostaglandin derivative

25. An ophthalmological composition according to claim 23 containing 1-10 µg of the prostaglandin derivative.

Claims for the following Contracting States : ES, GR

1. Use of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:

wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group
R_2 is a

(i) phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and a phenyl group; or

(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

for the preparation of an ophthalmological composition for the treatment of glaucoma or ocular hypertension.

2. Use according to claim 1 wherein the prostaglandin derivative is an ester.

3. Use according to claim 1 or claim 2 wherein B is a single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

4. Use according to anyone of claims 1-3 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

5. Use according to claim 3 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

6. Use according to claim 5 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative or a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

7. Use according to claim 6 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative of PGA' or PGF.

8. Use according to claim 6 wherein the prostaglandin is a 15-dehydro-17-phenyl-18,19,20-trinor derivative of PGA or PGF

9. Use according to claim 2, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

10. Use according to claim 2, wherein the prostaglandin derivative is 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

11. Use according to claim 2, wherein the prostaglandin derivative is 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-alkyl ester with 1-10 carbon atoms.

12. Use according to claim 2, wherein the prostaglandin derivative is 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

13. Use according to claim 2, wherein the prostaglandin derivative is 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

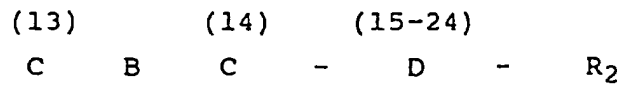
14. Use according to anyone of Claims 9 to 13, wherein the ester of the prostaglandin derivative is the isopropylester.

15. 13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

16. 15-dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester

17. 13,14-dihydro-17-phenyl-18,19,20-trinor-PGA_2-isopropylester.

18. Method for producing an ophthalmological composition for topical treatment of glaucoma or ocular hypertension comprising admixing an effective intraocular pressure reducing amount of a therapeutically active and physiologically acceptable derivative of prostaglandin PGA, PGB or PGF, in which the omega chain has the formula:



wherein
C is a carbon atom (the number is indicated within parenthesis)
B is a single bond, a double bond or a triple bond
D is a chain with 3 carbon atoms, optionally interrupted by hetero atoms O, S, or N, the substituents on each carbon atom selected from H, alkyl groups, preferably lower alkyl groups with 1-5 carbon atoms, a carbonyl group, or a hydroxyl group,
R_2 is

(i) a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, and phenyl group; or
(ii) an aromatic heterocyclic group having 5-6 ring atoms, like thiazol, imidazole, pyrrolidine, thiophene and oxazole;

and an ophthalmologically compatible carrier.

19. Method according to claim 18 wherein the prostaglandin derivative is an ester.

20. Method according to any one of claims 18-19 wherein B is single bond or a double bond and C_{15} being a carbonyl group or substituted with (R)-OH or (S)-OH.

21. Method according to any one of claims 18-20 wherein R_2 is a phenyl group which is unsubstituted or has at least one substituent selected from C_1-C_5 alkyl groups, C_1-C_4 alkoxy groups, trifluoromethyl groups, C_1-C_3 aliphatic acylamino groups, nitro groups, halogen atoms, or a phenyl group.

22. Method according to claim 20 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor derivative.

23. Method according to claim 22 wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor derivative.

24. Method according to claim 22 wherein the prostaglandin derivative is a 15-dehydro-17-phenyl-18,19,20-trinor derivative.

25. Method according to claim 19 wherein the prostaglandin derivative is a 17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

26. Method according to claim 19 wherein the prostaglandin derivative is a 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkyl ester with 1-10 carbon atoms.

27. Method according to claim 19, wherein the prostaglandin derivative is a 13,14-dihydro-17-phenyl-18,19,20-trinor-PGF_2 α-alkyl ester with 1-10 carbon atoms.

28. Method according to any one of claims 18 to 27 wherein the ester of the prostaglandin derivative is the isopropyl-ester.

29. Method according to anyone of claims 18 to 27 wherein the amount of prostaglandin derivative is 0.1-30 µg.

30. Method according to claim 29 wherein the amount of prostaglandin derivative is 1-10 µg.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die Formel

(13) (14)

C B C - D - R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 oder 2, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

5. Verwendung nach Anspruch 3, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

6. Verwendung nach Anspruch 5, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat ist.

7. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat von PGA oder PGF ist.

8. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA oder PGF ist.

9. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

10. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

11. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGA_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

12. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach einem der Ansprüche 9 bis 13, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

15. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

16. 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

17. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester.

18. Ophthalmologisches Präparat zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, umfassend eine wirksame, den Augeninnendruck reduzierende Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die folgende Formel

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterozyklische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

in einem ophthalmologisch verträglichen Träger.

19. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester ist.

20. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester ist.

21. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester ist.

22. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

23. Ophthalmologisches Präparat nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat der 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropylester ist.

24. Ophthalmologisches Präparat nach einem der Ansprüche 18 bis 22, umfassend 0,1-30 µg des Prostaglandinderivats.

25. Ophthalmologisches Präparat nach Anspruch 23, umfassend 1-10 µg des Prostaglandinderivats.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verwendung eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die Formel

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterocyclische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

zur Herstellung eines ophthalmologischen Präparats zur Behandlung von Glaucom oder erhöhtem Augendruck.

2. Verwendung nach Anspruch 1, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

3. Verwendung nach einem der Ansprüche 1 oder 2, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung ist, und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

4. Verwendung nach einem der Ansprüche 1 bis 3, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

5. Verwendung nach Anspruch 3, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

6. Verwendung nach Anspruch 5, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat oder ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat ist.

7. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-Derivat von PGA oder PGF ist.

8. Verwendung nach Anspruch 6, **dadurch gekennzeichnet, daß** das Prostaglandin ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat von PGA oder PGF ist.

9. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

10. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

11. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19-20-trinor-$PGA_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

12. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

13. Verwendung nach Anspruch 2, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19-20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

14. Verwendung nach einem der Ansprüche 9 bis 13, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

15. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

16. 15-Dehydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$isopropylester.

17. 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGA_{2\alpha}$isopropylester.

18. Verfahren zur Herstellung eines ophthalmologischen Präparats zur topischen Behandlung von Glaucom oder erhöhtem Augendruck, umfassend Mischen einer wirksamen, den Augeninnendruck reduzierenden Menge eines therapeutisch wirksamen und physiologisch verträglichen Derivats von Prostaglandin PGA, PGB oder PGF, worin die Omega-Kette die folgende Formel

(13)		(14)		(15-24)		
C	B	C	-	D	-	R_2

besitzt, worin
C ein Kohlenstoffatom ist (die Zahl ist in Klammern angegeben);
B eine Einfachbindung, eine Doppelbindung oder eine Dreifachbindung ist;
D eine Kette mit 3 Kohlenstoffatomen, gegebenenfalls durch die Heteroatome O, S oder N unterbrochen, wobei die Substituenten an jedem Kohlenstoffatom aus H, Alkylgruppen, bevorzugt Niedrigalkylgruppen mit 1-5 Kohlenstoffatomen, einer Carbonylgruppe oder einer Hydroxylgruppe ausgewählt sind;
R_2

(i) eine Phenylgruppe, die unsubstituiert ist oder mindestens einen Substituenten, ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen und einer Phenylgruppe, besitzt, oder
(ii) eine aromatische heterocyclische Gruppe mit 5-6 Ringatomen, wie Thiazol, Imidazol, Pyrrolidin, Thiophen und Oxazol ist,

mit einem ophthalmologisch verträglichen Träger.

19. Verfahren nach Anspruch 18, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein Ester ist.

20. Verfahren nach einem der Ansprüche 18 und 19, **dadurch gekennzeichnet, daß** B eine Einfachbindung oder eine Doppelbindung und C_{15} eine Carbonylgruppe ist oder mit (R)-OH oder (S)-OH substituiert ist.

21. Verfahren nach einem der Ansprüche 18 bis 20, **dadurch gekennzeichnet, daß** R_2 eine Phenylgruppe ist, die substituiert ist oder mindestens einen Substituenten ausgewählt aus C_1-C_5-Alkylgruppen, C_1-C_4-Alkoxygruppen, Trifluormethylgruppen, C_1-C_3-aliphatischen Acylaminogruppen, Nitrogruppen, Halogenatomen oder einer Phenylgruppe, besitzt.

22. Verfahren nach Anspruch 20, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-Derivat ist.

23. Verfahren nach Anspruch 22, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-Derivat ist.

24. Verfahren nach Anspruch 22, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-Dehydro-17-phenyl-18,19,20-trinor-Derivat ist.

25. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 17-Phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

26. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 15-(R)-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

27. Verfahren nach Anspruch 19, **dadurch gekennzeichnet, daß** das Prostaglandinderivat ein 13,14-Dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-alkylester mit 1-10 Kohlenstoffatomen ist.

28. Verfahren nach einem der Ansprüche 18 bis 27, **dadurch gekennzeichnet, daß** der Ester des Prostaglandinderivats der Isopropylester ist.

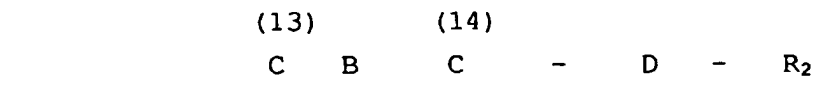
29. Verfahren nach einem der Ansprüche 18 bis 27, umfassend 0,1-30 µg des Prostaglandinderivats.

30. Verfahren nach Anspruch 29, umfassend 1-10 µg des Prostaglandinderivats.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle

C représente un atome de carbone (le numéro est inscrit entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes 0, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou

(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes

nitro, des atomes d'halogènes ou un groupe phényle.

5. Utilisation suivant la revendication 3, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

6. Utilisation suivant la revendication 5, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

7. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA ou PGF.

8. Utilisation suivant la revendication 6, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA ou PGF.

9. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

10. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

11. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant l'une quelconque des revendications 9 à 13, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

15. Ester isopropylique de 13,14-dihydro-17-phényl-18, 19, 20-trinor-$PGF_{2\alpha}$.

16. Ester isopropylique de 15-déshydro-17-phényl-18, 19, 20-trinor-$PGF_{2\alpha}$.

17. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

18. Composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, qui comprend une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :

dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 3 atomes de carbone, interrompue facultativement par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino

aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

dans un véhicule ophtalmologiquement compatible.

19. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

20. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

21. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

22. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

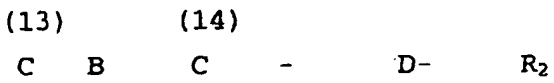
23. Composition ophtalmologique suivant la revendication 18, dans laquelle le dérivé de prostaglandine est l'ester isopropylique de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

24. Composition ophtalmologique suivant l'une quelconque des revendications 18 à 22, contenant 0,1 à 30 µg du dérivé de prostaglandine.

25. Composition ophtalmologique suivant la revendication 23, contenant 1 à 10 µg du dérivé de prostaglandine.

Revendications pour les Etats contractants suivants : ES, GR

1. Utilisation d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :



dans laquelle
C représente un atome de carbone (le numéro est indiqué entre parenthèses),
B représente une liaison simple, une double liaison ou une triple liaison,
D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,
R_2 représente

(i) un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

pour la préparation d'une composition ophtalmologique destinée au traitement du glaucome ou de l'hypertension oculaire.

2. Utilisation suivant la revendication 1, dans laquelle le dérivé de prostaglandine est un ester.

3. Utilisation suivant la revendication 1 ou la revendication 2, dans laquelle B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou est substitué avec un groupe (R)-OH ou (S)-OH.

4. Utilisation suivant l'une quelconque des revendications 1 à 3, dans laquelle R_2 représente un groupe phényle qui est non substitué ou qui possède au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes ou un groupe phényle.

5. Utilisation suivant la revendication 3, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 17-phényl-18,19,20-trinor.

6. Utilisation suivant la revendication 5, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor ou un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

7. Utilisation suivant la revendication 6, dans laquelle le dérivé de prostaglandine est un dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor de PGA ou PGF.

8. Utilisation suivant la revendication 6, dans laquelle la prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor de PGA ou PGF.

9. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

10. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-déshydro-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

11. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

12. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

13. Utilisation suivant la revendication 2, dans laquelle le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

14. Utilisation suivant l'une quelconque des revendications 9 à 13, dans laquelle l'ester du dérivé de prostaglandine est l'ester isopropylique.

15. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF2α.

16. Ester isopropylique de 15-dihydro-17-phényl-18,19,20-trinor-PGF2α.

17. Ester isopropylique de 13,14-dihydro-17-phényl-18,19,20-trinor-PGA_2.

18. Procédé de production d'une composition ophtalmologique destinée au traitement topique du glaucome ou de l'hypertension oculaire, comprenant le mélange d'une quantité, à effet de réduction de la pression intraoculaire, d'un dérivé, thérapeutiquement actif et physiologiquement acceptable, de prostaglandine PGA, PGB ou PGF, dans lequel la chaîne oméga répond à la formule :

dans laquelle

C représente un atome de carbone (le numéro est indiqué entre parenthèses),

B représente une liaison simple, une double liaison ou une triple liaison,

D représente une chaîne ayant 3 atomes de carbone, facultativement interrompue par des hétéro-atomes O, S ou N, les substituants sur chaque atome de carbone étant choisis entre H, des groupes alkyle, de préférence des groupes alkyle inférieurs ayant 1 à 5 atomes de carbone, un groupe carbonyle et un groupe hydroxyle,

R_2 représente

(i) un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et le groupe phényle ; ou
(ii) un groupe hétérocyclique aromatique ayant 5 ou 6 atomes dans le cycle, tel que les groupes thiazole, imidazole, pyrrolidine, thiophène et oxazole ;

et un véhicule ophtalmologiquement compatible.

19. Procédé suivant la revendication 18, dans lequel le dérivé de prostaglandine est un ester.

20. Procédé suivant l'une quelconque des revendications 18 et 19, dans lequel B représente une liaison simple ou une double liaison et C_{15} représente un groupe carbonyle ou bien est substitué avec un groupe (R)-OH ou (S)-OH.

21. Procédé suivant l'une quelconque des revendications 18 à 20, dans lequel R_2 représente un groupe phényle qui est non substitué ou qui porte au moins un substituant choisi entre des groupes alkyle en C_1 à C_5, des groupes alkoxy en C_1 à C_4, des groupes trifluorométhyle, des groupes acylamino aliphatiques en C_1 à C_3, des groupes nitro, des atomes d'halogènes et un groupe phényle.

22. Procédé suivant la revendication 20, dans lequel le dérivé de prostaglandine est le dérivé à fonction 17-phényl-18,19,20-trinor.

23. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est le dérivé à fonction 13,14-dihydro-17-phényl-18,19,20-trinor.

24. Procédé suivant la revendication 22, dans lequel le dérivé de prostaglandine est un dérivé à fonction 15-déshydro-17-phényl-18,19,20-trinor.

25. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

26. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'alkyle en C_1 à C_{10} de 15-(R)-17-phényl-18,19,20-trinor-$PGF_{2\alpha}$.

27. Procédé suivant la revendication 19, dans lequel le dérivé de prostaglandine est un ester d'α-alkyle en C_1 à C_{10} de 13,14-dihydro-17-phényl-18,19,20-trinor-PGF_2.

28. Procédé suivant l'une quelconque des revendications 18 à 27, dans lequel l'ester du dérivé de prostaglandine est l'ester isopropylique.

29. Procédé suivant l'une quelconque des revendications 18 à 27, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 0,1 à 30 µg.

30. Procédé suivant la revendication 29, dans lequel la quantité de dérivé de prostaglandine est comprise dans l'intervalle de 1 à 10 µg.